



PCT/EP 03/07127

REC'D 12 SEP 2003	
WIPO	PCT



INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

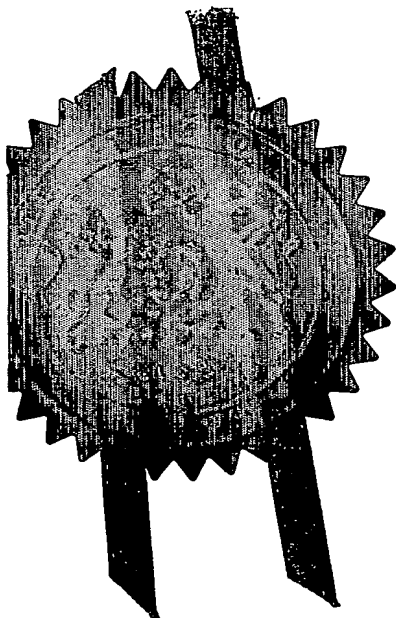
PCT/EP03/7127

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed *Paul Brown*

Dated 23 May 2003

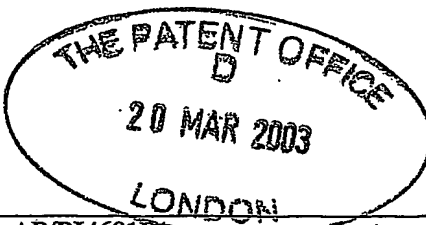
The
Patent
Office

21MAR03 E793 976-1 D01030
P01/7700 0.00-0306454.0

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)



The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your Reference

AP/PI4681PI

2. Patent application number

(The Patent office will fill in this part)

0306454.0

12 0 MAR 2003

3. Full name, address and postcode of the or of each applicant (underline all surnames)

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number (if you know it)

473587003

If the applicant is a corporate body, give the country/state of its corporation

GB

4 Title of the invention

CHEMICAL COMPOUNDS

5 Name of your agent (if you know one)

PETER DOLTON

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY
CN925.1
980 GREAT WEST ROAD
BRENTFORD
MIDDLESEX
TW8 9GS, GB

Patents ADP number (if you know it)

8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of Filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? (Answer yes if:

YES

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form -

Description 62

Claim(s) 3

Abstract 1

Drawing(s) -

10. If you are also filing any of the following, state how many against each item

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

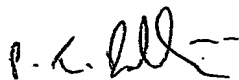
Request for preliminary examination and search (Patent Form 9/77)

Request for substantive examination (Patent Form 10/77)

Any other documents (please specify)

11.

I/We request the grant of a patent on the basis of this application



Signature PETER DOLTON 19 March 2003
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY
020 8047 4420

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the patent Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been received

a) Notes

If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form

If you have answered "Yes" Patents Form 7/77 will need to be filed.

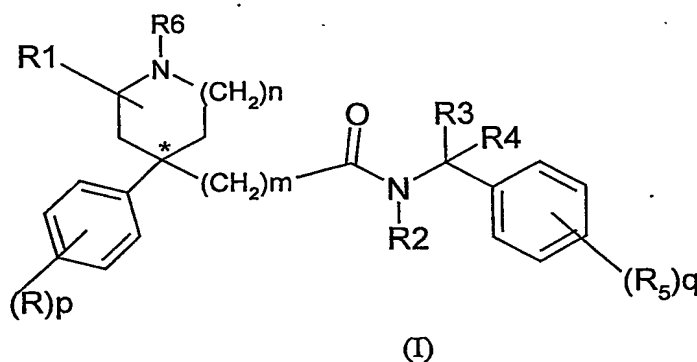
d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

Chemical Compounds

The present invention relates to cyclic amine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

The present invention thus provides compounds of formula (I)



wherein

R represents halogen, C₁₋₄ alkyl, cyano, C₁₋₄ alkoxy, trifluoromethyl or trifluoromethoxy;
 R₁ represents hydrogen, halogen, cyano, C₁₋₄ alkyl optionally substituted by halogen, or C₁₋₄ alkoxy;

R₂ represents hydrogen, or C₁₋₄ alkyl;

R₃ and R₄ independently represent hydrogen, cyano, C₁₋₄ alkyl or R₃ together with the R₄ represents C₃₋₇ cycloalkyl;

R₅ represents trifluoromethyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, trifluoromethoxy or halogen, cyano;

R₆ represents hydrogen or (CH₂)_rR₇;

R₇ represents hydrogen, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, amine, C₁₋₄ alkylamine, (C₁₋₄ alkyl)₂amine, OC(O)NR₉R₈ or C(O)NR₉R₈;

R₉ and R₈ independently represent hydrogen, C₁₋₄ alkyl or C₃₋₇ cycloalkyl;

m represents zero or an integer from 1 to 4;

n represents 1 or 2;

p is zero or an integer from 1 to 3;

q is zero or an integer from 1 to 3;

r is an integer from 1 to 4;

and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g.

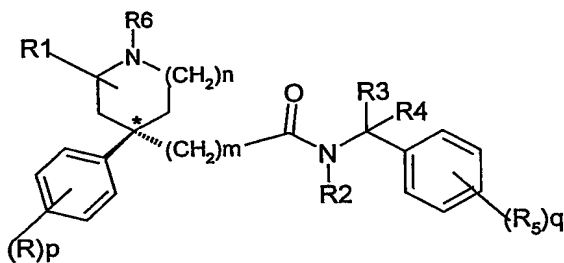
methanesulphonates or p-toluenesulphonates), phosphates, trifluoroacetates, acetates, citrates, succinates, tartrates, lactates, malates, fumarates and maleates.

The solvates may, for example, be hydrates.

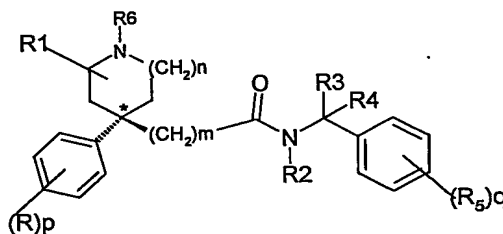
5

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts and their pharmaceutically acceptable solvates.

- 10 It will be appreciated by those skilled in the art that the compounds of formula (I) provided that when n is 1 and R_1 is not hydrogen or n is 2 contain at least one chiral centre (namely the carbon atom shown as * in formula (I)) and may be represented by formula (1a) and (1b).



(1a)

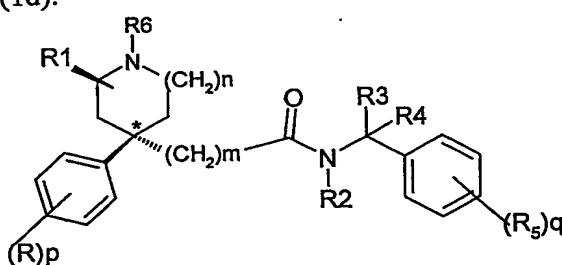


(1b)

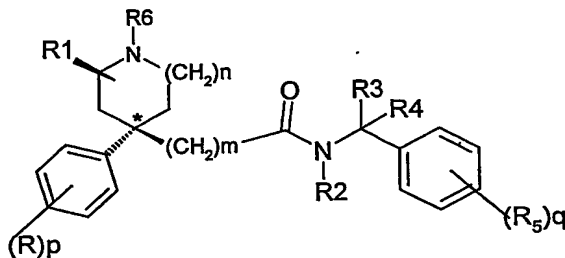
15

The wedge bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

- 20 At least two asymmetric carbon atoms are present in the compounds of formula (I) when R_1 is different from hydrogen (namely the carbon atom shown as * in formula (I) and the carbon atom to which the group R_1 is attached) and may be represented by formula (1a) (1b), (1c) and (1d).

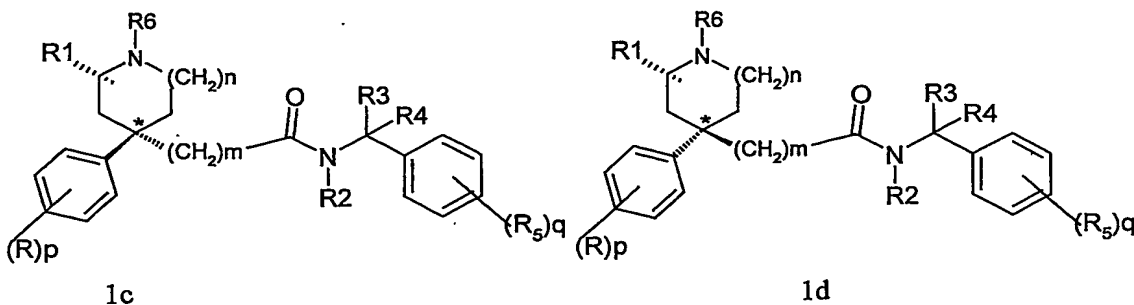


1a



1b

25



The configuration of the chiral carbon atoms of the compounds shown in 1a and 1d is hereinafter referred to as syn configuration and in formulae 1b and 1c as the anti configuration.

Further asymmetric carbon atoms are possible when R₃ and R₄ are not the same group.

It is to be understood that all stereoisomeric forms including all enantiomers and mixtures thereof are encompassed within the scope of the present invention and the reference to compound of formula (I) include all stereoisomeric forms unless otherwise stated.

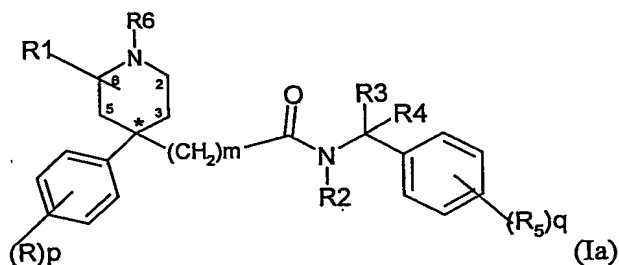
The term C₁₋₄ alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, 1 methylethyl or 2-methyl propyl.

The term halogen refers to fluorine, chlorine, bromine or iodine.

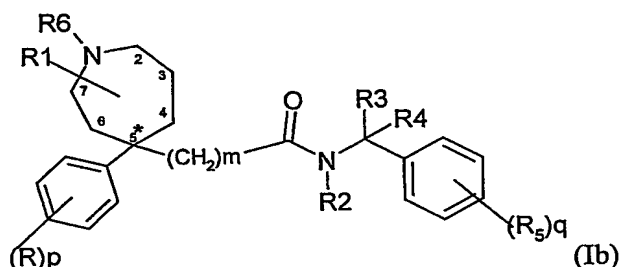
The term C₃₋₇ cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term C₁₋₄ alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

In the compounds of formula (I) wherein n is 1 the group R₁ may be in position 2, 3, 5 or 6 of the piperidine ring as represented in formula (1a)



In the compounds of formula (I) wherein n is 2 the group R₁ may be in position 2, 3, 5, 6 or 7 of the ring as represented in formula (Ib)



R is preferably halogen (e.g. fluorine) and/or a C₁₋₄ alkyl (e.g. methyl) group and p is preferably 0 or an integer from 1 to 2.

R₁ is preferably hydrogen, halogen (e.g. fluorine) or methyl.

R₂ is preferably hydrogen or methyl.

R₃ is preferably hydrogen or methyl.

R₄ is preferably hydrogen, methyl or together with R₃ is cyclopropyl.

R₅ is preferably trifluoromethyl, cyano, methyl, chlorine, bromine or fluorine atom and q is preferably an integer from 1 to 2.

Preferred compounds according to the invention are:

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-

methyl-acetamide;

N-[1-(3,5-Dichloro-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-

methyl-acetamide;

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-(1-methyl-4-phenyl-piperidin-4-yl)-N-methyl-acetamide;

N-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide;

5 N-(3,5-Dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;

4-(4-Fluorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide;

4-(4-Chlorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide;

10 4-(4-Fluorophenyl)-piperidine-4-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;

N-(3,5-Bis-trifluoromethyl)-benzyl-2-[(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide

15 N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluorophenyl)-azepin-4-yl]-N-methyl-acetamide;

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-

20 methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

25 enantiomers thereof and pharmaceutically acceptable salts thereof (e.g. hydrochloride).

The compounds of the invention are antagonists of tachykinin receptors, including substance P and other neurokinins, both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

30

Tachykinins are a family of peptides that share a common carboxyl-terminal sequence (Phe-X-Gly-Leu-Met-NH₂). They are actively involved in the physiology of both lower and advanced lifeforms. In mammalian lifeforms the main tachykinins are substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB) which act as neurotransmitters and neuromodulators. Mammalian tachykinins may contribute to the pathophysiology of a number of human diseases.

35

Three types of tachykinins receptors have been identified, namely NK1(SP-preferring), NK2 (NKA-preferring) and NK3 (NKB-preferring) which are widely distributed throughout the central nervous (CNS) and peripheral nervous system.

- 5 Particularly the compounds of the invention are antagonists of the NK1 receptor.

The compounds of the present invention also have activity as selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) and are thus of use in the treatment of conditions mediated by selective inhibition of the serotonin reuptake transporter protein.

10

Thus, the compounds of the present invention combine dual activity as tachykinin antagonists, including substance P and other neurokinins, and as SSRIs. In particular, the compounds of the invention combine dual activity as NK1 receptor antagonists and as SSRIs.

- 15 NK₁-receptor binding affinity has been determined in vitro by measuring the compounds' ability to displace [³H] - substance P (SP) from recombinant human NK₁ receptors expressed in Chinese Hamster Ovary (CHO) cell membranes.

CHO cell membranes were prepared by using a modification of the method described by Beattie D.T. et al. (Br. J. Pharmacol, 116:3149-3157, 1995). Briefly, ligand binding was
20 performed in 0.2 ml of 50 mM HEPES, pH 7.4, containing 3 mM MnCl₂, 0.02% BSA, 0.5 nM [³H]-Substance P (30÷56 Ci/mmol, Amersham), a final membrane concentration of 20÷30 µg of protein/ml, and the test compounds. The incubation proceeded at room temperature for 40 min and stopped by filtration. Non-specific binding was determined using excess of substance P (1 µM) and represents about 6÷10% of the total binding.

- 25 Compounds of the invention were further characterised in a functional assay for the determination of their effect to inhibit the intracellular calcium increase induced by SP in Human-NK₁-CHO cells using FLIPR technology. Briefly, after 30min incubation with the cytoplasmic calcium indicator Fluo-4 AM (2µM), cells were washed and incubated in the absence or presence of three different concentrations of antagonist for 60min, at 37°C in
30 Hank's balanced salts with 20mM Hepes, and then non-cumulative concentration-response curves of SP (2pM-300nM) was performed. The potency of the antagonist (pK_B value) was calculated from Schild's analysis.

- 35 The action of the compounds of the invention at the NK₁ receptor and/or serotonin transporter may be determined by using conventional animal models. Thus, the ability to bind at the NK₁ receptor and/or serotonin transporter was determined using the guinea pig pup isolation calls model as described by Pettijohn, Psychol. Rep., 1979 and Rupniak et al., Neuropharmacology, 2000.

Human Serotonin Transporter (hSERT) binding affinity has been determined in vitro by the compounds' ability to displace [^3H]- Imipramine from human serotonin transporter expressed in Human Embryonic Kidney HEK293 cell membranes (Receptor Biology Inc.). For the binding reaction, 4 nM of [^3H]- Imipramine (703 GBq/mmol, Amersham) were incubated with 0.02 mg/ml of cell membrane and the compound to be tested at different concentrations (7 concentration points) in 50 mM Tris HCl, pH 7.5, 120 mM of NaCl and 5 mM KCl. The reaction was performed for 60 min at 4°C and was terminated by through GF/B Unifilter (pre-soaked in 0.5 % PEI) using a Cell Harvester (Packard). Scintillation fluid was added to each filtered spot and radioactivity was determined using a scintillation counter (TopCount (Packard)). Non-specific binding was determined using Imipramine (100 μM) and represents about 5% of the total binding.

For the preferred compounds of the invention Human Serotonin Transporter binding affinity has been also determined in vitro by the compounds ability to displace [^3H] paroxetine.

Competition experiments were conducted with duplicate determination for each point.

Msat601 software package was used to elaborate the competition binding data.

IC_{50} values were converted to K_i values using Cheng-Prusoff equation.

The inhibitory activity of the compounds at the rat serotonin transporter has been determined in vitro using rSERT-LLCPK cells (LLCPK cells transfected with the rat SERT). The cells have been plated onto 96-well plates (60000 cells/well). After 24 hr, cells have been washed in uptake buffer (Hank's balanced salt solution + 20 mM Hepes) and pre-incubated for 10 min at RT with 50 μl of buffer containing the test compounds. 50 μl of 50 nM [^3H] Serotonin (5HT) solution (final concentration: 25 nM [^3H] 5HT) have been added and plates have been incubated for 7 min at RT, during which cells take up radiolabelled 5HT. Aspirating the solution and rapidly washing the cells with cold buffer has terminated the uptake.

The amount of radioactive 5HT incorporated in the cells has been then measured by adding the scintillation cocktail directly onto the cells and reading the plate in the Top Count. The data have been digitally processed to obtain the pIC_{50} values of the antagonists. The pK_i values have been calculated using the Chen-Prusoff equation.

Compounds of the invention are useful in the treatment of CNS disorders and psychotic disorders, in particular in the treatment or prevention of depressive states and /or in the treatment of anxiety as defined in, but not restricted to, Diagnostic Statistical of Mental Disorder (DSM) IV edition edit by American Psychiatric Association and International Classification Diseases 10th revision (ICD10).

Thus, for example, depressive states include Major Depressive Disorders (MDD), including bipolar depression, unipolar depression, single or recurrent major depressive episodes, recurrent brief depression, with or without psychotic features, catatonic features, melancholic features including anorexia, weight loss, atypical features, anxious depression, cyclothymic or postpartum onset.

Other mood disorders encompassed within the term major depressive disorders include dysthymic disorders with early or late onset and with or without atypical features, neurotic depression, post-traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

The term anxiety includes anxiety disorders, such as panic disorders with or without agoraphobia, agoraphobia, phobias, for example, social phobias or agoraphobia, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorders, generalised anxiety disorders, acute stress disorders and mixed anxiety-depression disorders.

Compounds of the invention are useful as analgesics. In particular, they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmenorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondylitis; gout; burns; scar pain; itch and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of the cognitive disorders. Cognitive disorders include dementia, amnesic disorders and cognitive disorders not otherwise specified.

- 5 Furthermore, compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

10 Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds) or in the treatment of tolerance to and dependence on opiates (e.g. cannabis, heroin, morphine) or benzodiazepines; in the treatment of addiction to cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof.

15 Compounds of the invention are also useful as anti-inflammatory agents. In particular, they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

20 Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

30 Compounds of the invention are also useful in the treatment or prevention of schizophrenic disorders including paranoid schizophrenia, disorganised schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, residual schizophrenia.

35 Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine

and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intracranial pressure; decreased intracranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease (GERD) such as erosive GERD and symptomatic GERD or non erosive GERD, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn, dyspepsia and functional dyspepsia.

Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome, gastro-oesophageal reflux disease (GERD) such as erosive GERD and symptomatic GERD or non erosive GERD, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn, dyspepsia and functional dyspepsia (such as ulcer-like dyspepsia, dysmotility-like dyspepsia and unspecified dyspepsia) chronic constipation; skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischaemia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

The compounds of the invention are also useful in premenstrual dysphoric disorder (PMDD), in chronic fatigue syndrome and Multiple sclerosis.

Compounds of the invention have been found to exhibit anxiolytic and antidepressant activity in conventional tests. For example, in Guinea pig pups separation-induced vocalisations (Molewijk et al., 1996).

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of serotonin reuptake.

5

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

10

In a further aspect there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of depression and /or anxiety.

15

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins and/or by selective inhibition of the serotonin reuptake transporter protein comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

20

In a further aspect of the present invention is provided a method for the treatment of a mammal, including man, in particular in the treatment of depression and /or anxiety which method comprises administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

25

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

30

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

35

Thus, compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

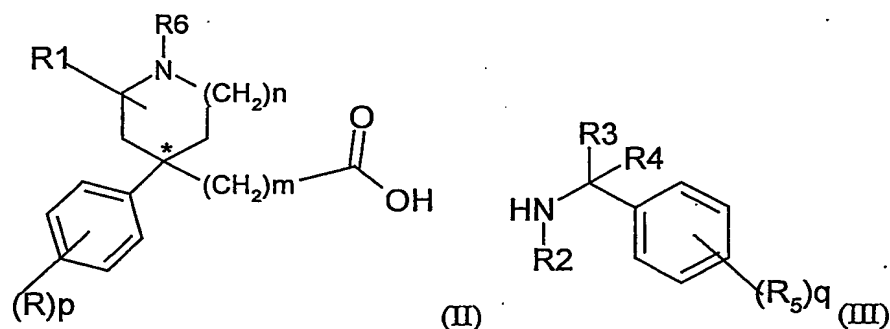
For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

Thus, for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range 1 to 300 mg e.g. 1 to 100 mg.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R₁, R₂, R₃, R₄, R₅, m, n, p and q have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

Compounds of formula (I) may be prepared by reaction of an activated derivative of the carboxylic acid (II), wherein R₆ is nitrogen protecting group or (CH₂)_rR₇, with amine (III)



wherein R_2 is hydrogen, C_{1-4} alkyl or nitrogen protecting group, followed where necessary by removal of any nitrogen protecting group.

5

Suitable activated derivatives of the carboxyl group include the acyl halide, mixed anhydride, activated ester such as thioester or the derivative formed between the carboxylic acid group and a coupling agent such as that used in peptide chemistry, for example carbonyl diimidazole or dicyclohexylcarbodiimide.

- 10 The reaction is preferably carried out in an aprotic solvent such as hydrocarbon, halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran.

The activated derivatives of the carboxylic acid (II) may be prepared by conventional means. A particular suitable activated derivative for use in this reaction is O-(Benzotriazol-1-yl) - N,N,N',N'-tetramethyluronium tetrafluoroborate.

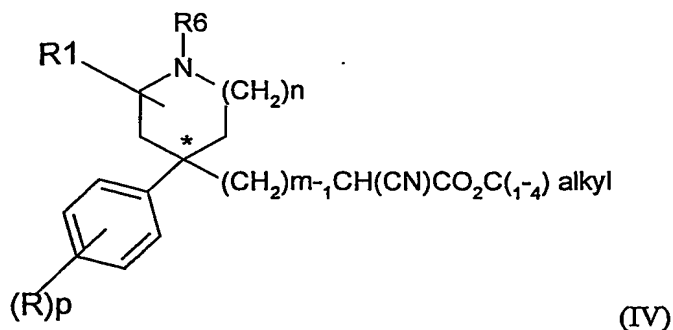
- 15 The reaction is suitably carried out in a solvent such as NN-dimethylformamide.

Compounds of formula(I), wherein R_2 is C_{1-4} alkyl may be prepared by reaction of a compound of formula(I), in which R_2 is hydrogen, with $(C_{1-4} \text{ alkyl})L$ wherein L is a suitable leaving group selected from iodine, bromine.

- 20 The reaction is conveniently carried out in a solvent such as NN-dimethylformamide or tetrahydrofuran.

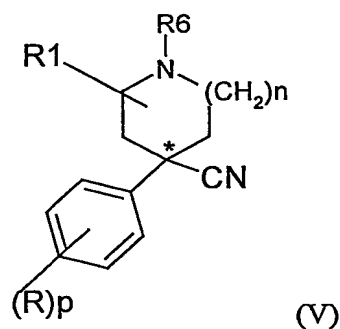
Compounds of formula (II), wherein m is an integer from 1 to 4, may be prepared by reaction of a cyano derivative (IV) with an acid such as for example concentrated sulfuric acid. The

- 25 The reaction is conveniently carried out in a solvent such as acetic acid and heating the reaction mixture up to 150° .



Compounds of formula (II), wherein m is zero, may be prepared by hydrolysis of a cyano derivative (V) in the presence of a base such as alkaline base (i.e potassium hydroxide).

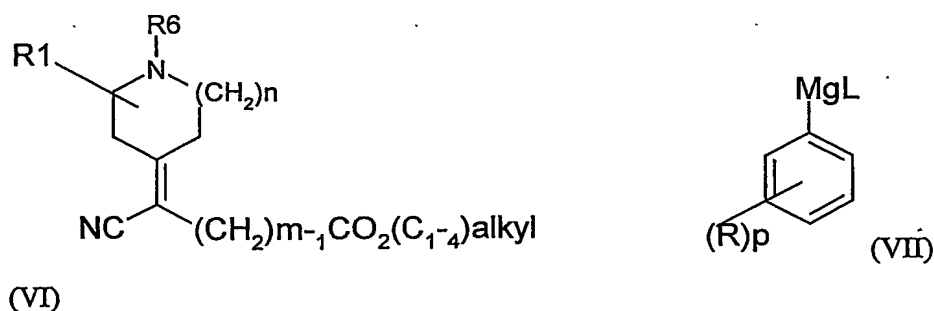
5



The reaction is suitably carried out in aqueous solvent and with heating.

Compounds of formula (IV) may be prepared by reaction of a compound of formula (VI) with a compound of formula (VII), wherein L is a halogen group (i.e bromine).

10

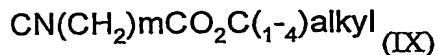
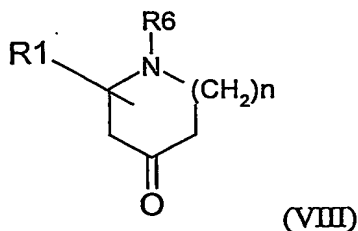


The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon (e.g toluene), ethers (e.g tetrahydrofuran) and at a temperature within the range 0-25°C, optionally in the presence of Copper(I) salts such as for example Copper Iodide.

15

Compounds of formula (VI) may be prepared by reaction of a compounds of formula (VIII) with a cyano derivative (IX).

20



Compounds of formulae (V) and (VIII) may be prepared with analogous methods to those used for known compounds. Thus, compounds of formula (V) may be prepared according to the procedure described in Cammack et al., Heterocyclic 23,73 (1986).

Compounds of formula (VIII) may be prepared according to the procedure described in WO 2001/000206.

When R_6 and/or R_2 are a nitrogen protecting group, examples of suitable groups include alkoxy carbonyl e.g. t-butoxycarbonyl, benzyloxycarbonyl, arylsulphonyl e.g. phenylsulphonyl or 2-trimethylsilylethoxymethyl.

Protection and deprotection may be effected using conventional techniques such as those described in "Protective Groups in Organic Synthesis 2nd Ed." by T.W. Greene and P. G. M. Wuts (John Wiley and Sons, 1991) and as described in the examples hereinafter.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods.

Thus, for example, specific enantiomers of the compounds of formula (I) may be obtained from the corresponding enantiomeric mixture of a compound of formula (I) using chiral HPLC procedure.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein. Thus, in a one embodiment of the invention the enantiomers of the compound of formula (I) may be prepared by reaction of a chiral amine (III) using any of the processes described above for preparing compounds of formula (I) from amine (III).

The chiral amine (III) may be prepared from the corresponding racemic amine (III) using any conventional procedures such as salt formation with a suitable optically active acid such as for example di-p-toluoyl-D-tartaric acid or di-p-toluoyl-L-tartaric acid, or using chiral HPLC procedure.

Where it is desired to isolate a compound of formula (I) as a salt, for example a pharmaceutically acceptable salt, this may be achieved by reacting a compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether, *tert*-butylmethyl ether or tetrahydrofuran).

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Buchi m.p. apparatus and are uncorrected. R.T. or r.t. refer to room temperature.

Infrared spectra (IR) were measured in chloroform or nujol solutions on a FT-IR instrument.

Proton Magnetic Resonance (NMR) spectra were recorded on Varian instruments at 400 or 500 MHz, chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, double; t, triple; q, quartet; m, multiplet; b, broad. Mass spectra (MS) were taken on a VG Quattro mass spectrometer.

Optical rotations were determined at 20°C with a Jasco DIP360 instrument (l=10 cm, cell volume = 1 mL, λ = 589 nm). Flash silica gel chromatography was carried out over silica gel 230-400 mesh supplied by Merck AG Darmstadt, Germany. T.l.c. refers to thin layer chromatography on 0.25 mm silica gel plates (60F-254 Merck) and visualized with UV light. For phase separations performed by using microfiltration device: phase separation cartridge with polypropylene frit by Whatman and Alltech. For purifications carried out by using SCX:

SCX-cartridges (loading 0.75mmol/g) by Varian.

Solutions were dried over anhydrous sodium sulphate.

Methylene chloride was redistilled over calcium hydride and tetrahydrofuran was redistilled over sodium.

The following abbreviations are used in the text: AcOEt = ethyl acetate, CH = cyclohexane, DCM = methylene chloride, DIPEA = N,N-diisopropylethylamine, DMF = N,N'-dimethylformamide, Et₂O = diethyl ether, EtOH = ethanol, MeOH = methanol TEA = triethylamine, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

Enantiomer 1 or enantiomer 2 means a compound of the invention or an intermediate thereof as a single enantiomer whose configuration was not determined.

Anti isomer means a compound of the invention or intermediate thereof wherein the group R₁ is different from hydrogen and with reference to the plane of paper it is on the opposite site of the phenyl attached to the cyclic amine ring.

Intermediate 1

4-[(1-Cyano-1-ethoxycarbonyl)-methylene]-piperidine-1-carboxylic acid *tert*-butyl ester

Method A

A round bottom flask equipped with a Dean Stark apparatus was charged with *tert*-butyl-4-oxo-1-piperidine carboxylate (1.0 g), ethyl cyanoacetate (0.587 mL), ammonium acetate

(0.193 g) and acetic acid (0.286 mL) in anhydrous benzene (20 mL). The mixture was heated to reflux overnight, then it was allowed to cool to r.t. and washed with water (20 mL). The aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic extracts were washed with a 1M sodium hydroxide solution (10 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (1.5 g) as a yellow oil.

Method B

Ethyl cyanoacetate (13.9 mL), ammonium acetate (4.64 g) and acetic acid (6.9 mL) were added, under a Nitrogen atmosphere, to a solution of *tert*-butyl-4-oxo-1-piperidine carboxylate (20 g) in anhydrous toluene (200 mL) in a round bottom flask equipped with a Dean Stark apparatus. The mixture was heated to 110°C for 2 hours, then to 85°C overnight and finally to 130°C for 4 hours. The mixture was allowed to cool to r.t. and washed with 1M sodium hydroxide solution, water and brine. The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (15.54 g) as a yellow oil.

T.l.c.: CH/AcOEt 8:2, R_f=0.35 (detection with ninhydrine).

IR (nujol, cm⁻¹): 2229 (C≡N), 1720 and 1694 (C=O).

NMR (CDCl₃): □ (ppm) 4.29 (q, 2H); 3.61 (t, 2H); 3.55 (t, 2H); 3.13 (t, 2H); 2.78 (t, 2H); 1.49 (s, 9H); 1.36 (t, 3H).

MS (ES/+): m/z=295 [M+H]⁺.

Intermediate 2

4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

25

Method A

A solution of intermediate 1 (1.5 g) in anhydrous toluene (15 mL) was dropped over 30 minutes into a solution of 4-fluorophenyl magnesium bromide (2M in Et₂O – 6.1 mL) in anhydrous Et₂O (50 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and left at this temperature for 2 days. The mixture was treated with 3N sulfuric acid solution (5 mL), water (30 mL) and AcOEt (10 mL). The layers were separated and the aqueous phase was extracted with further AcOEt (2 x 30 mL). The combined organic layers were washed with a saturated sodium hydrogen carbonate (60 mL) and water (60 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (0.448 g) as a yellow oil.

35

Method B

A solution of 4-fluorophenyl magnesium bromide (1.0M in THF, 49 mL) was added dropwise to a mixture of intermediate 1 (8 g) and copper iodide (1.57 g) in anhydrous THF (65 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was stirred under these conditions for 1 hour and then allowed to warm to r.t. and stirred at 23°C for 2 hours.

5 The mixture was cooled to 0°C, treated with 3M hydrochloric acid solution until pH=5 and extracted with AcOEt (3 x 100 mL). The combined organic extracts were washed with a saturated ammonium chloride solution (200 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 85:15) to give the title compound (9.8 g) as a yellow oil.

10 T.l.c.: CH/AcOEt 6:4, Rf=0.35 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.31 (dd, 2H); 7.06 (t, 2H); 3.95 (q, 2H); 3.87 (bs, 2H); 3.54 (t, 1H); 2.85 (bt, 2H); 2.53 (dt, 2H); 1.9 (m, 2H); 1.4 (s, 9H); 1.02 (t, 3H).

MS (ES/+): m/z=391 [M+H]⁺.

15 Intermediate 3

4-Carboxymethyl-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (

20 A mixture of intermediate 2 (0.448 g) in acetic acid (2 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C overnight. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (50 mL). Then, di-*tert*-butyl-dicarbonate (500 mg) was added and the resulting mixture was stirred at r.t. for 5 hours. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=1 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (210 mg) as a pale yellow
25 foam.

T.l.c.: CH/AcOEt 1:1, Rf=0.25 (detection with ninhydrine).

NMR (d₆-DMSO): δ (ppm) 11.78 (bs, 1H); 7.4 (dd, 2H); 7.15 (t, 2H); 3.45 (m, 2H); 3.11 (m, 2H); 2.54 (s, 2H); 2.04 (m, 2H); 1.89 (m, 2H); 1.37 (s, 9H).

30 Intermediate 4

4-([(3,5-Dichlorobenzyl)methylcarbamoyl]methyl)-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

35 3,5-Dichlorobenzyl-methylamine (37 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (37 mg) and 1-hydroxybenzotriazole (26 mg) were added to a solution of intermediate 3 (60 mg) in anhydrous DMF (2 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL), 0.005M hydrochloric acid solution (15 mL) and a saturated sodium hydrogen carbonate solution (15 mL). The organic layer was dried, concentrated *in vacuo* and the

residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (80 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.35 (detection with ninhydrine).

NMR (d₆-DMSO – 70°C): □ (ppm) 7.37 (m, 3H); 7.03 (m, 4H); 4.28 (bs, 2H); 3.48 (m, 2H); 3.12 (m, 2H); 2.71 (bs, 2H); 2.57 (s, 3H); 2.2-1.9 (m, 4H); 1.38 (s, 9H).

Intermediate 5

3-Fluoro-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester

Trimethylsilyl trifluoromethanesulfonate (2.17 mL) was added to a solution of *tert*-butyl-4-oxo-1-piperidine carboxylate (2.0 g) and TEA (3.34 mL) in anhydrous DCM (20 mL) previously cooled to -30°C under a Nitrogen atmosphere. The mixture was stirred at this temperature for 1 hour, then it was quickly treated with cold saturated sodium hydrogen carbonate solution (20 mL). The layers were separated and the organic phase was dried and concentrated *in vacuo* to give 1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydro-4-pyridinyl-trifluoromethanesulfonate as a yellow oil, which was dissolved in anhydrous acetonitrile (80 mL) and the resulting solution was treated with Selectfluor (3.89 g). The mixture was stirred at r.t. for 1 hour, then it was concentrated *in vacuo* and the residue was dissolved in AcOEt (50 mL). The organic layer was washed with a saturated sodium hydrogen solution (30 mL), dried and concentrated *in vacuo* to a residue, which was purified by chromatography on neutral Alumina Brochmann type 1 (initially AcOEt then AcOEt/MeOH 95:5) to give the title compound (0.99 g) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.3 (detection with ninhydrine).

NMR (d₆-DMSO): □ (ppm) 5.08 (dd, 1H); 4.32 (bm, 1H); 4.0 (bm, 1H); 3.19 (m, 2H); 2.56 (m, 1H); 2.36 (m, 1H); 1.43 (s, 9H).

Intermediate 6

4-(1-Cyano-1-ethoxycarbonyl-methylene)-3-fluoro-piperidine-1-carboxylic acid *tert*-butyl ester

A round bottom flask equipped with a Dean Stark apparatus was charged with intermediate 5 (0.99 g), ethyl cyanoacetate (0.534 mL), ammonium acetate (0.176 g) and acetic acid (0.261 mL) in anhydrous benzene (20 mL). The mixture was heated to reflux overnight, then it was allowed to cool to r.t. and washed with water (20 mL). The aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic extracts were washed with a 1M sodium hydroxide solution, dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (0.696 g – *cis/trans* mixture) as a yellow oil.

T.l.c.: CH/AcOEt 7:3, R_f=0.45 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 6.49 and 5.55 (2bd, 1H); 4.54 (bm, 1H); 4.34 (bm, 3H); 3.72 (m, 1H); 3.12 (bm, 1H); 2.9 (bm, 1H); 2.74 (m, 1H); 1.49 (s, 9H); 1.38 (t, 3H).

Intermediate 7

5 4-(1-Cyano-1-ethoxycarbonyl-methyl)-3-fluoro-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester 8 (anti isomer)

A solution of intermediate 6 (0.696 g) in anhydrous toluene (5 mL) was dropped over 30 minutes into a solution of 4-fluorophenyl magnesium bromide (2M in Et₂O – 2.67 mL) in anhydrous Et₂O (15 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and stirred at this temperature overnight. The mixture was treated with 3N sulfuric acid solution (3 mL), water (10 mL) and AcOEt (25 mL). The layers were separated and the aqueous phase was extracted with further AcOEt (2 x 30 mL). The combined organic layers were washed with a saturated sodium hydrogen carbonate (60 mL) and water (60 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (0.383 g) as a yellow oil.

T.l.c.: CH/AcOEt 8:2, R_f=0.27 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.5-6.8 (m, 4H); 4.8 (bm, 2H); 4.5-3.5 (bm; 3H); 3.85 (s, 1H); 3.2-2.4 (bm, 2H); 2.2 (bm, 2H); 1.4 (s, 9H); 1.05 (2t, 3H).

20 Intermediate 8

4-Carboxymethyl-3-fluoro-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (anti isomer)

A mixture of intermediate 7 (0.383 g) in acetic acid (2 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C overnight. The solution was allowed to cool to r.t. and dropped into a 3M sodium hydroxide solution (50 mL). Then, di-*tert*-butyl-dicarbonate (409 mg) was added and the resulting mixture was stirred at r.t. overnight. It was cooled to 0°C and treated with 3M hydrochloric acid solution until pH=1 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (96 mg) as a pale yellow oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.5 (detection with ninhydrine).

NMR (d₆-DMSO): δ (ppm) 11.89 (bs, 1H); 7.46 (dd, 2H); 7.16 (t, 2H); 5.36 (dd, 1H); 3.96 (bm, 1H); 3.75 (bm, 1H); 3.2-2.6 (bm, 3H); 2.5 (m, 1H); 2.36 (bd, 1H); 1.93 (bm, 1H); 1.38 (s, 9H).

35 Intermediate 9

4-[[[(3,5-Dichlorobenzyl)-methylcarbamoyl]-methyl]-3-fluoro-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (anti isomer)

3,5-Dichlorobenzyl-methylamine (53 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (53 mg) and 1-hydroxybenzotriazole (38 mg) were added to a solution of intermediate 8 (90 mg) in anhydrous DMF (4 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (20 mL) and washed with water (15 mL), 0.005M hydrochloric acid solution (15 mL) and a saturated sodium hydrogen carbonate solution (15 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (62 mg) as a white foam.

T.l.c.: CH/AcOEt 7:3, R_f=0.30 (detection with ninhydrine).

10 NMR (d₆-DMSO – 60°C): δ (ppm) 7.42 (m, 3H); 7.08 (m, 2H); 6.98 (bs, 2H); 5.58-5.5 (bd, 1H); 4.28 (m, 2H); 3.99 (m, 1H); 3.75 (bm, 1H); 3.0 (bm, 1H); 2.89 (d, 1H); 2.79 (bm, 1H); 2.68 (d, 1H); 2.64-2.57 (2bs, 1H); 2.4 (bm, 1H); 2.04-1.98 (2bm, 1H); 1.38 (s, 9H).

Intermediate 10

15 3,4-Dimethoxybenzyl chloride

A solution of 3,4-dimethoxy-benzyl alcohol (1.5 g) in anhydrous DCM (5 mL) was dropped into a solution of thionyl chloride (1.3 mL) in anhydrous DCM (6 mL) under a Nitrogen atmosphere. The solution was heated to reflux for 1 hour, then allowed to cool to r.t. and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (1.63 g) as a white solid.

T.l.c.: CH/AcOEt 6:4, R=0.63.

NMR (CDCl₃): δ (ppm) 7.94 (dd, 1H); 6.92 (d, 1H); 6.83 (d, 1H); 4.57 (s, 2H); 3.9 (s, 3H); 3.89 (s, 3H).

MS (EI/+): m/z=186 [MH]⁺.

Intermediate 11

Bis-(2-hydroxyethyl)-3,4-diemthoxybenzylamine

Intermediate 10 (1.38 g) was added to a mixture of diethanolamine (0.71 mL) and potassium carbonate (1.12 g) in anhydrous toluene (13 mL) previously heated to 60°C under a Nitrogen atmosphere. The resulting mixture was heated to reflux for 1 hour, then allowed to cool to r.t., filtered off and the organic phase was concentrated *in vacuo* to give the title compound (1.87 g) as a yellow oil.

NMR (CDCl₃): δ (ppm) 6.85 (dd, 1H); 6.8 (d, 2H); 3.9 (2s, 6H); 3.6 (s, 2H); 3.55 (dd, 4H); 2.6-2.7 (d, 4H).

Intermediate 12

Bis-(2-chloroethyl)-3,4-dimethoxybenzylamine

A solution of thionyl chloride (1.37 mL) in anhydrous DCM (7 mL) was dropped into a solution of intermediate 10 (1.85 g) in anhydrous DCM (11 mL) under a Nitrogen atmosphere. The solution was heated to reflux for 3 hour, then allowed to cool to r.t. and concentrated *in vacuo*. The residue was triturated from Et₂O to give the title compound (2.08 g) as a whitish solid.

NMR (CDCl₃): δ (ppm) 7.6 (s, 1H); 6.9 (d, 1H); 6.8 (d, 1H); 4.25 (s, 2H); 4.1-3.95 (m, 4H); 3.92 (s, 3H); 3.85 (s, 3H); 3.5-3.4 (m, 4H).

Intermediate 13

10 1-(3,4-Dimethoxybenzyl)-4-(4-fluorophenyl)-4-cyanopiperidine hydrochloride

Intermediate 12 (1.41 g) and hexadecyltributyl phosphonium bromide (104 mg) were added to a mixture of 4-fluoroacetonitrile (0.488 mL) in a 50% sodium hydroxide solution (10 mL). The mixture was heated to reflux for 1 hour, then it was allowed to cool to r.t., then a 6M hydrochloric acid solution was added until acidic pH and the mixture was extracted with AcOEt (3 x 30 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue, which was triturated with AcOEt to give the title compound (1.017 g) as a whitish solid.

IR (nujol, cm⁻¹): 1609 (C=C).

NMR (d₆-DMSO): δ (ppm) 10.72 (bs, 1H); 7.56 (m, 2H); 7.35 (m, 3H); 7.11 (d, 1H); 7.02 (d, 1H); 4.37 (d, 2H); 3.8 (s, 3H); 3.77 (s, 3H); 3.52 (bm, 2H); 3.18 (bm, 2H); 2.46 (bm, 4H).

MS (ES/+): m/z=355 [MH-HCl]⁺.

Intermediate 14

4-(4-Fluorophenyl)-4-cyanopiperidine

25 Method A:

Intermediate 13 (150 mg) was treated with a 3M potassium hydroxide solution (20 mL) and extracted with AcOEt (2 x 20 mL). The combined organic extracts were dried and concentrated *in vacuo* to give 1-(3,4-dimethoxybenzyl)-4-(4-fluorophenyl)-4-cyanopiperidine (136 mg). Cerium ammonium nitrate (842 mg) was added to a solution of this compound (136 mg) in acetonitrile (4.3 mL) and water (0.48 mL). The mixture was stirred at r.t. for 21 hour, then it was concentrated *in vacuo*. The residue was triturated with a 20% sodium hydroxide solution (20 mL), the inorganic salts were filtered off and the aqueous phase was extracted with AcOEt (4 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (AcOEt/MeOH 6:4 + 1% TEA) to give the title compound (46 mg) as a yellow oil.

35 Method B:

A mixture of intermediate 26 (1.36 g) and 10% palladium over charcoal (0.42 g) in EtOH (12.8 mL) and acetic acid (0.13 mL) was hydrogenated at 4.5 atm. for 4 hours. The mixture

was filtered over celite and the solution was concentrated *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeOH 8:2) to give the title compound (0.71 g) as a yellow oil.

T.l.c.: AcOEt/MeOH 8:2, R_f=0.09 (detection with ninhydrine).

5 NMR (d₆-DMSO): δ (ppm) 7.56 (m, 2H); 7.27 (t, 2H); 3.04 (m, 2H); 2.8 (m, 2H); 2.01 (m, 2H); 1.84 (m, 2H).

MS (ES/+): m/z=205 [MH]⁺.

Intermediate 15

10 4-(4-Fluorophenyl)-piperidine-4-carboxylic acid hydrochloride

A solution of intermediate 14 (100 mg) in a 3M potassium hydroxide solution (6.6 mL) was heated to reflux for 21 hours. The solution was allowed to cool to r.t. and acidified with conc. hydrochloric acid until pH=2. The solid obtained was filtered off and the aqueous layer was concentrated *in vacuo*. The residue was treated with MeOH; the alcoholic solution was

15 filtered off and concentrated *in vacuo* to give the title compound (106 mg) as a brown solid.

NMR (d₆-DMSO): δ (ppm) 13.0 (bs, 1H); 8.85-8.95 (bm, 2H); 7.55-7.45 (m, 2H); 7.3-7.2 (m, 2H); 3.35 (m, 2H); 2.95-2.85 (bm, 2H); 2.5 (m, 2H); 2.05 (m, 2H).

MS (ES/+): m/z=224 [MH-HCl]⁺.

20 Intermediate 16

1-(tert-Butoxycarbonyl)-4-(4-fluorophenyl)-piperidine-4-carboxylic acid

TEA (0.33 mL) and di-*tert*-butyl-dicarbonate (0.52 g) were added to a solution of intermediate 15 (0.56 g) in anhydrous DMF (21 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 16 hours, then AcOEt was added (50 mL) and the mixture was washed with 2.5% hydrochloric acid solution (30 mL). The organic phase was dried and concentrated *in vacuo* to give the title compound (0.683 g) as a brown oil.

T.l.c.: DCM/MeOH 94:6, R_f=0.62 (detection with ninhydrine).

25 NMR (CDCl₃): δ (ppm) 7.45-7.35 (m, 2H); 7.15-7.05 (m, 2H); 4.35-4.2 (bm, 2H); 3.25-3.1 (m, 2H); 2.07-2.02 (m, 2H); 1.92-1.84 (m, 2H); 1.45 (s, 9H).

30

Intermediate 17

[(3,5-Bis-trifluoromethylbenzyl)-methylcarbamoyl]-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl

A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (53 mg), 1-hydroxybenzotriazole (37 mg), intermediate 16 (80 mg) and TEA (35 μ L) in anhydrous DCM (3 mL) was stirred at r.t. for 20 hours under a Nitrogen atmosphere, then TEA (90 μ L) and 3,5-bis(trifluorobenzyl)-methylamine (182 mg) were added. The mixture was stirred at r.t. for 48 hours, then it was washed with a 5% sodium hydrogen carbonate solution (2 x 5

mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (36.7 mg) as a white solid.

T.l.c.: CH/AcOEt 6:4, R_f=0.48.

IR (nujol, cm⁻¹): 1678 (C=O), 1614 (C=C).

5 NMR (d₆-DMSO - 70°C): □ (ppm) 7.92 (bs, 1H); 7.74 (bs, 2H); 7.32 (m, 2H); 7.13 (t, 2H); 4.64 (bs, 2H); 3.76 (m, 2H); 3.12 (m, 2H); 2.61 (s, 3H); 2.35 (m, 1H); 1.83 (m, 1H); 1.41 (s, 9H).

MS (ES/+): m/z=563 [MH]⁺.

10 Intermediate 18

4-(4-Chlorophenyl)-4-cyano-1-(3,4-dimethoxybenzyl)-piperidine hydrochloride

Intermediate 12 (2 g) and hexadecyltributyl phosphonium bromide (147.2 mg) were added to a mixture of 4-chlorophenylacetonitrile (0.88 g) in a 50% sodium hydroxide solution (8.7 mL). The mixture was heated to reflux for 1 hour, then it was allowed to cool to r.t.. A 6M
15 hydrochloric acid solution was added until acidic pH and the mixture was extracted with AcOEt (3 x 30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give the title compound (1.75 g) as a whitish solid.

NMR (d₆-DMSO): □ (ppm) 10.52 (bs, 1H); 7.8-7.7 (m, 4H); 7.35 (m, 1H); 7.21-7.15 (d, 1H); 7.05-7.0 (d, 1H); 4.37 (d, 2H); 3.8 (s, 6H); 3.77-3.6 (m, 2H); 3.3 (s, 3H); 3.2-3.05 (bm, 2H);
20 2.75-2.55 (bm, 2H); 2.46 (bm, 2H).

Intermediate 19

4-(4-Chlorophenyl)-4-cyanopiperidine

Intermediate 18 (1.5 g) was treated with a 3M potassium hydroxide solution (100 mL) and
25 extracted with AcOEt (2 x 80 mL). The combined organic extracts were dried and concentrated *in vacuo* to give 4-(4-chlorophenyl)-4-cyano-1-(3,4-dimethoxybenzyl)piperidine (1.3 g). Cerium ammonium nitrate (7.69 g) was added to a solution of this compound (1.3 g) in acetonitrile (40 mL) and water (4.4 mL). The mixture was stirred at r.t. for 15 hours, then it was concentrated *in vacuo*. The residue was triturated with a 20% sodium hydroxide solution
30 (80 mL), the inorganic salts were filtered off and the aqueous phase was extracted with AcOEt (4 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (AcOEt/MeOH 6:4 + 1% TEA) to give the title compound (210 mg) as a brown solid.

T.l.c.: AcOEt/MeOH 6:4 + 1% TEA, R_f=0.22 (detection with ninhydrine).

35 NMR (d₆-DMSO): □ (ppm) 7.5 (m, 4H); 3.25-3.1 (m, 3H); 2.95-2.85 (m, 2H); 2.2-2.1 (bm, 2H); 2.05-1.97 (bm, 2H).

MS (ES/+): m/z=221 [MH]⁺.

Intermediate 20**4-(4-Chlorophenyl)-piperidine-4-carboxylic acid hydrochloride**

A solution of intermediate 19 (177 mg) in a 3M potassium hydroxide solution (10.7 mL) was heated to reflux for 21 hours. The solution was allowed to cool to r.t. and acidified with conc. hydrochloric acid until pH=2. The solid obtained was filtered off; the aqueous layer was concentrated *in vacuo* to half volume and cooled to 0°C. The solid precipitated was filtered off to give the title compound (147 mg) as a brown solid.

IR (nujol, cm⁻¹): 1712 (C=O).

NMR (d₆-DMSO): δ (ppm) 13.1 (bs, 1H); 8.62 (bs, 2H); 7.47 (m, 2H); 7.4 (m, 2H); 3.23 (m, 2H); 2.94 (m, 2H); 2.49 (m, 2H); 2.05 (m, 2H).

MS (ES/+): m/z=240 [MH-HCl]⁺.

Intermediate 21**1-(tert-Butoxycarbonyl)-4-(4-chlorophenyl)-piperidine-4-carboxylic acid**

DIPEA (0.1 mL) and di-*tert*-butyl-dicarbonate (126.3 mg) were added to a solution of intermediate 20 (145 mg) in anhydrous DMF (5.3 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 24 hours, then AcOEt was added (20 mL) and the mixture was washed with 1M hydrochloric acid solution (20 mL). The organic phase was dried and concentrated *in vacuo* to give the title compound (145 mg) as a brown oil.

T.l.c.: DCM/MeOH 94:6, R_f=0.5 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.4-7.25 (m, 2H); 7.0-6.95 (m, 2H); 4.15-4.0 (bm, 2H); 3.1-2.9 (m, 2H); 2.07-2.6 (m, 2H); 1.92-1.8 (m, 2H); 1.45 (s, 9H).

Intermediate 22**[(3,5-Bis-trifluoromethylbenzyl)-methylcarbamoyl]-(4-chlorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester**

A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (91 mg), 1-hydroxybenzotriazole (64 mg), intermediate 21 (145 mg) and TEA (66 μ L) in anhydrous DCM (5 mL) was stirred at r.t. for 12 hours under a Nitrogen atmosphere, then TEA (160 μ L) and 3,5-bis(trifluorobenzyl)-methylamine (315 mg) were added. The mixture was stirred at r.t. for 48 hours, then it was washed with a 5% sodium hydrogen carbonate solution (2 x 5 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (18 mg) as a white solid.

T.l.c.: CH/AcOEt 6:4, R_f=0.45.

NMR (CDCl₃): δ (ppm) 7.85 (bm, 1H); 7.65 (s, 1H); 7.6-7.5 (m, 1H); 7.39-7.3 (d, 2H); 7.2-7.15 (d, 2H); 4.63-4.5 (bm, 2H); 4.0-3.85 (m, 2H); 3.26 (m, 2H); 3.0 (m, 2H); 2.65 (s, 3H); 2.35 (m, 2H); 1.45 (s, 9H).

Intermediate 23**[(3,5-Dichlorobenzyl)-methylcarbamoyl]-(4-fluorophenyl)-piperidine-1-carboxylic acid
tert-butyl ester**

DIPEA (162 □L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (126 mg) were added to a solution of intermediate 16 (100 mg) in anhydrous DMF (12 mL) under a Nitrogen atmosphere. After stirring for 1 hour, 3,5-dichlorobenzyl-methylamine hydrochloride (140 mg) was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH₂Cl₂/AcOEt 8:2) to give the title compound (82 mg) as a colourless oil.

T.l.c.: AcOEt, R_f=0.72.

IR (nujol, cm⁻¹): 1678 (C=O), 1614 (C=C).

NMR (d₆-DMSO - 70°C): □ (ppm) 7.49 (m, 1H); 7.3 (m, 4H); 7.15 (bm, 2H); 4.44 (bs, 2H); 3.79 (bd, 2H); 3.07 (bm, 2H); 2.54 (bs, 3H); 2.31 (bd, 2H); 1.77 (bt, 2H); 1.39 (s, 9H).

MS (ES/+): m/z=495 [MH]⁺.

Intermediate 24**Bis-(2-hydroxyethyl)-benzylamine**

Benzylbromide (13.91 mL) was added to a mixture of diethanolamine (11 mL) and potassium carbonate (17.79 g) in anhydrous toluene (190 mL) previously heated to 60°C under a Nitrogen atmosphere. The resulting mixture was heated to reflux for 1 hour, then further benzylbromide (6.95 mL) was added, and the mixture refluxed for further 3 hours. The mixture was allowed to cool to r.t., filtered and the organic phase was concentrated *in vacuo* to give the title compound (22.8 g) as a yellow oil.

T.l.c.: AcOEt/MeOH 9:1, R_f=0.58 (detection with ninhydrine).

NMR (CDCl₃): □ (ppm) 7.5-7.1 (m, 5H); 4.2 (bm, 1H); 3.67 (s, 2H); 3.55 (t, 4H); 3.43 (bm, 1H); 2.64 (t, 4H).

Intermediate 25**Bis-(2-chloroethyl)-benzylamine**

A solution of thionyl chloride (20.49 mL) in anhydrous DCM (300 mL) was dropped into a solution of intermediate 24 (22.8 g) under a Nitrogen atmosphere. The solution was heated to reflux for 5 hour, then allowed to cool to r.t. and concentrated *in vacuo*. The residue was triturated from AcOEt to give the title compound (23.81 g) as a whitish solid.

NMR (CDCl₃): □ (ppm) 7.7 (m, 2H); 7.45 (m, 3H); 4.4 (s, 2H); 4.1-4.0 (m, 4H); 3.55-3.45 (t, 4H).

Intermediate 26

1-Benzyl-4-(4-fluorophenyl)-4-cyanopiperidine

Intermediate **25** (23.81 g) and hexadecyltributyl phosphonium bromide (2.15 g) were added to a mixture of 4-fluoroacetonitrile (10.14 mL) in a 50% sodium hydroxide solution (128 mL). The mixture was heated to reflux for 2 hours, then it was allowed to cool to r.t. A 6M hydrochloric acid solution was added until acidic pH and the mixture was extracted with AcOEt (3 x 100 mL). The combined organic extracts were dried and concentrated *in vacuo*. The solid so obtained was dissolved in a 1% sodium hydroxide solution and extracted with DCM. The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 1:1) to give the title compound (8.99 g) as a brown oil.

T.l.c.: CH/AcOEt 4:6, R_f=0.59 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.45 (m, 2H); 7.3 (m, 5H); 7.1-7.0 (t, 2H); 3.6 (s, 2H); 3.0 (d, 2H); 2.55-2.45 (m, 2H); 2.1-2.0 (m, 4H).

MS (ES/+): m/z=295 [MH]⁺.

Intermediate 27**4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester**

A solution of 2-bromo-5-fluorotoluene (10.8 mL) in anhydrous THF (40.5 mL) was dropped into a suspension of magnesium turning (2.2 g) and few crystals of iodine in anhydrous THF (21.5 mL) under a Nitrogen atmosphere. The mixture refluxed for 30 minutes, then it was allowed to cool to r.t. and added drop-wise to a mixture of intermediate **1** (8 g) and copper iodide (1.6 g) in anhydrous THF (66 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and stirred at 23°C for 1.5 hours. The mixture was cooled to 0°C, treated with 3M hydrochloric acid solution until pH=5 and extracted with AcOEt (3 x 100 mL). The combined organic extracts were washed with a saturated ammonium chloride solution (200 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (6.71 g) as a white foam.

T.l.c.: CH/AcOEt 8:2, R_f=0.17(detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.33 (dd, 1H); 7.07 (t, 1H); 7.0 (td, 1H); 4.48 (s, 1H); 3.99-3.81 (m, 4H); 2.72-2.53 (m, 4H); 2.46 (s, 3H); 1.86-1.74 (m, 2H); 1.36 (s, 9H); 0.94 (t, 3H).

MS (ES/+): m/z=427 [M+Na]⁺.

Intermediate 28**4-Carboxymethyl-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester**

A mixture of intermediate 27 (298 mg) in acetic acid (4.3 mL), conc. sulfuric acid (1.1 mL) and water (1.1 mL) was heated to 140°C for 5 hours. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (38 mL). Then, di-*tert*-butyl-dicarbonate (217.6 mg) was added and the resulting mixture was stirred at r.t. over week end. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=6-7 and then extracted with AcOEt (3 x 20 mL). The organic phase was washed with brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 8:2 to 6:4) to give the title compound (131 mg) as a white solid.

T.l.c.: CH/AcOEt 6:4, Rf=0.12 (detection with ninhydrine).

10 NMR (d_6 -DMSO): \square (ppm) 11.8 (bs, 1H); 7.28 (dd, 2H); 6.96 (dd, 1H); 6.91 (td, 1H); 3.4 (bm, 2H); 3.22 (bm, 2H); 2.7 (s, 2H); 2.47 (s, 3H); 2.1 (m, 2H); 2.01 (m, 2H); 1.37 (s, 9H).
MS (ES/+): m/z=374 [M+Na]⁺.

Intermediate 29

15 4-{[(3,5-Dichlorobenzyl)methylcarbamoyl]methyl}-4-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (91 \square L) and O-(benzotriazol-1-yl)-N,N,N'-tetramethyluronium tetrafluoroborate (54.6 mg) were added to a solution of intermediate 28 (46 mg) in anhydrous DMF (3.8 mL) under a Nitrogen atmosphere. After stirring for 30 minutes, 3,5-dichlorobenzyl-methylamine hydrochloride (59.3 mg) was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt and washed with 5% sodium hydrogen carbonate and brine. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt from 9:1 to 6:4) to give the title compound (34 mg) as a colourless oil.

T.l.c.: CH/AcOEt 6:4, Rf=0.16 (detection with ninhydrine).

25 IR (nujol, cm⁻¹): 1699 and 1643 (C=O).

NMR (d_6 -DMSO): \square (ppm) 7.42 (dd, 1H); 7.24 (dd, 1H); 6.98 (d, 2H); 6.88 (dd, 1H); 6.83 (td, 1H); 4.26 (s, 2H); 3.45-3.08 (m, 4H); 2.23-1.99 (m, 4H); 2.81 (s, 3H); 2.58 (s, 2H); 2.41 (s, 3H); 1.33 (s, 9H).

MS (ES/+): m/z=545 [M+Na]⁺.

30

Intermediate 30

4-{[(3,5-Bis-trifluoromethyl-benzyl)methylcarbamoyl]methyl}-4-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (241 \square L) and O-(benzotriazol-1-yl)-N,N,N'-tetramethyluronium tetrafluoroborate (144.4 mg) were added to a solution of intermediate 28 (122 mg) in anhydrous DMF (10 mL) under a Nitrogen atmosphere. After stirring for 30 minutes, 3,5-bis(trifluorobenzyl)-methylamine hydrochloride (293.5 mg) was added. The mixture was stirred at r.t. for 2 hours, then it was diluted with AcOEt and washed with 5% sodium hydrogen carbonate and brine.

The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH₂Cl₂/AcOEt from 9:1 to 1:1) to give the title compound (159 mg) as a colourless oil.

T.l.c.: CH₂Cl₂/AcOEt 6:4, R_f=0.1 (detection with ninhydrine).

5 IR (nujol, cm⁻¹): 1737 and 1638 (C=O).

NMR (d₆-DMSO): δ (ppm) 7.98 (s, 1H); 7.74 (s, 1H); 7.21 (dd, 1H); 6.87 (dd, 1H); 6.74 (td, 1H); 4.47 (s, 2H); 3.49 (m, 2H); 3.1 (m, 2H); 2.87 (s, 2H); 2.67 (s, 3H); 2.42 (s, 3H); 2.23 (m, 2H); 2.02 (m, 2H); 1.36 (s, 9H).

MS (ES/+): m/z=613 [M+Na]⁺.

10

Intermediate 31

5-Ethoxycarbonyl-4-oxo-azepine-1-carboxylic acid *tert*-butyl

15 Ethyl diazoacetate (6.84 mL) and boron trifluoride diethyl etherate (6.34 mL) were added simultaneously over 1 hour to a suspension of *tert*-butyl-4-oxo-1-piperidine carboxylate (10.0 g) in dry Et₂O (60 mL) previously cooled to -25°C under a Nitrogen atmosphere. The solution obtained was stirred at -25°C for 1 hour, then it was allowed to warm to 0°C and stirred at 0°C for 1 hour. The solution was treated with a saturated potassium carbonate solution (10 mL). The layers were separated; the organic phase was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (petroleum/Et₂O 6:4) to give the title compound (11.58 g) as a colourless oil.

20

T.l.c.: petroleum/Et₂O 1:1, R_f=0.48 (detection with phosphomolybdic acid).

IR (nujol, cm⁻¹): 1744 and 1695 (C=O).

NMR (d₆-DMSO): δ (ppm) 4.08 (q, 3H); 3.82-3.64 (m, 2H); 3.38 (m, 2H); 2.64 (m, 2H); 1.9-1.64 (m, 2H); 1.36 (s, 9H); 1.16 (t, 3H).

25

MS (ES/+): m/z=286 [MH]⁺.

Intermediate 32

Azepin-4-one hydrochloride

30 A suspension of intermediate 31 (11.58 g) in 3M hydrochloric acid (60 mL) was heated to reflux for 7 hours. The mixture was allowed to cool to r.t. and concentrated *in vacuo*. The residue was triturated with abs. EtOH (10 mL) to give the title compound (4.54 g) as a white solid.

M.p.: 189-191°C.

35

NMR (d₆-DMSO): δ (ppm) 9.17 (bs, 2H); 3.3 (m, 2H); 3.22 (m, 2H); 2.75 (m, 2H); 2.62 (m, 2H); 1.93 (m, 2H).

Intermediate 33

4-Oxo-azepine-1-carboxylic acid *tert*-butyl ester

Di *tert*-butyl dicarbonate (0.7 g) was added to a suspension of intermediate 32 (0.4 g) and TEA (0.45 mL) in anhydrous DCM (5 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was stirred for 1 hour at 0°C then it was allowed to reach r.t.. The mixture was treated with a saturated ammonium chloride solution (10 mL) and extracted with further DCM (2 x 10 mL). The combined organic extracts were washed with water, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (528 mg) as a colourless oil.

T.l.c.: CH/AcOEt 6:4, R_f=0.3 (detection with ninhydrine).

NMR (d₆-DMSO): □ (ppm) 3.53 (bm, 2H); 3.45 (bm, 2H); 2.58 (m, 2H); 2.52 (m, 2H); 1.61 (bm, 3H); 1.37 (s, 9H).

Intermediate 34

4-(1-Cyano-1-ethoxycarbonyl-methylene)-azepine-1-carboxylic acid *tert*-butyl ester

A round bottom flask equipped with a Dean Stark apparatus was charged with intermediate 33 (1.87 g), ethyl cyanoacetate (1.03 mL), methyl ammonium acetate (0.339 g) and acetic acid (0.5 mL) in anhydrous benzene (15 mL). The mixture was heated to reflux overnight, then it was allowed to cool to r.t. and washed with water (10 mL). The aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic extracts were washed with a 1M sodium hydroxide solution (10 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (2.49 g – cis/trans mixture) as a colourless oil.

T.l.c.: CH/AcOEt 8:2, R_f=0.25 (detection with ninhydrine).

NMR (d₆-DMSO): □ (ppm) 4.23 (q, 2H); 3.57 (t, 1H); 3.51 (t, 1H); 3.37 (m, 2H); 3.18 (t, 1H); 2.96 (m, 2H); 2.77 (m, 1H); 1.7 (m, 2H); 1.39-1.36 (m, 9H); 1.28-1.21 (m, 6H).

Intermediate 35

4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluorophenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A solution of intermediate 34 (0.5 g) in anhydrous toluene (5 mL) was dropped over 30 minutes into a solution of 4-fluorophenyl magnesium bromide (2M in Et₂O – 1.95 mL) in anhydrous Et₂O (15 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and left at this temperature for 2 days. The mixture was treated with 3N sulfuric acid solution (5 mL), water (10 mL) and AcOEt (15 mL). The layers were separated and the aqueous phase was extracted with further AcOEt (2 x 15 mL). The combined organic layers were washed with a saturated sodium hydrogen carbonate (30 mL) and water (30 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (331 mg) as a colourless oil.

T.l.c.: CH/AcOEt 8:2, R_f=0.30 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.3 (m, 2H); 7.05 (m, 2H); 4.0 (bm, 2H); 4.2-2.5 (bm, 4H); 3.4 (s, 1H); 2.4-1.5 (bm, 6H); 1.4 (s + t, 12H).

Intermediate 36

5 4-Carboxymethyl-4-(4-fluorophenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate 35 (0.33 g) and a 15% potassium hydroxide solution in ethylene glycol (7 mL) was heated to 180°C overnight. The solution was allowed to cool to r.t., diluted with water (5 mL), cooled at 0°C and acidified with 15% hydrochloric acid until pH=1. The glycol-aqueous phase was distilled off (70°C/2 mbar) to leave a brown residue which was
10 further dried (140°C/2 mbar for 1 hour) to give a mixture of 4-carboxymethyl-4-(4-fluorophenyl)-azepine and potassium chloride (700 mg).

Sodium hydroxide (24 mg) and di-*tert*-butyl-dicarbonate (60 mg) were added to a part of this material (80 mg) suspended in water (5 mL). The solution was stirred at r.t. overnight, then it was cooled to 0°C and treated with 0.1M hydrochloric acid solution until pH=1 and extracted
15 with Et₂O (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 1:1) to give the title compound (17 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.25 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.25 (m, 2H); 6.95 (t, 2H); 3.8-3.4 (m, 2H); 3.2 (m, 2H); 2.6 (s,
20 2H); 2.5 (m, 3H); 2.3 (m, 1H); 2.0-1.5 (m, 2H); 1.4 (bs, 9H).

Intermediate 37

4-[(3,5-Bis-trifluoromethyl-benzyl)methylcarbamoyl]-methyl}-4-(4-fluorophenyl)-azepine-1-carboxylic acid *tert*-butyl ester

25 3,5-(Bis-trifluoromethyl-benzyl)-methylamine (14 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10 mg) and 1-hydroxybenzotriazole (7 mg) were added to a solution of intermediate 36 (17 mg) in anhydrous DMF (2 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL), 0.005M hydrochloric acid solution (10 mL) and a saturated sodium
30 hydrogen carbonate solution (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (18 mg) as a colourless oil.

T.l.c.: CH/AcOEt 6:4, R_f=0.4.

NMR (d₆-DMSO – 70°C): δ (ppm) 7.93 (bs, 1H); 7.78 (bs, 2H); 7.31 (m, 2H); 6.97 (bt, 2H);
35 4.51 (m, 2H); 3.51 (bm, 1H); 3.35 (bm, 1H); 3.15 (m, 2H); 2.71 (s, 3H); 2.7 (m, 2H); 2.48 (m, 1H); 2.26 (m, 1H); 2.04 (m, 1H); 1.87 (m, 1H); 1.69 (m, 1H); 1.51 (1H); 1.35 (s, 9H).

Intermediate 38

4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A small amount of iodine and 3 drops of methyl iodide were added to a suspension of magnesium turnings (655 mg) in dry Et₂O (15 mL), at r.t., under a Nitrogen atmosphere, then the mixture was vigorously refluxed. 2-Bromo-5-fluoro-toluene (3.1 mL) was added over 1 hour to this mixture followed by further Et₂O (5 mL). The suspension was heated under vigorous reflux for 1.5 hours, then further Et₂O (40 mL) was added. A solution of intermediate 34 (2.5 g) in anhydrous Et₂O (10 mL) was added to the solution of Grignard so obtained over 30 minutes. The resulting solution was refluxed for further 30 minutes then it was cooled to 0°C, a 3M sulfuric acid solution (15 mL) and water (25 mL) were added and the aqueous layer was extracted with AcOEt (2 x 30 mL).

The combined organic extracts were washed with a saturated sodium hydrogen carbonate solution (50 mL) and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 8:2 to 6:4) to give the title compound (531 mg) as a white foam.

T.l.c.: CH/AcOEt 1:1, R_f=0.76 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.3 (m, 2H); 7.05 (m, 2H); 4.0 (bm, 2H); 4.2-2.5 (bm, 4H); 3.4 (s, 1H); 2.4-1.5 (bm, 6H); 1.4 (s + t, 12H).

Intermediate 39

4-Carboxymethyl-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate 38 (0.531 g) in acetic acid (3 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C overnight. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (50 mL). Then, di-*tert*-butyl-dicarbonate (277 mg) was added and the resulting mixture was stirred at r.t. for 5 hours. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=1 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (60 mg) as a pale yellow oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.35 (detection with ninhydrine).

NMR (d₆-DMSO): δ (ppm) 11.88 (bs, 1H); 7.3 (m, 1H); 6.99 (m, 1H); 6.91 (m, 1H); 3.6-3.0 (m, 4H); 2.6-2.4 (m, 2H); 2.45 (s, 3H); 2.6-2.4 (m, 2H); 2.05-1.9 (m, 2H); 1.8-1.4 (m, 2H); 1.3 (s, 9H).

Intermediate 40

4-[(3,5-Bis-trifluoromethyl-benzyl)methylcarbamoyl]-methyl-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

DIPEA (43 μ L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (34.3 mg) were added to a solution of intermediate **39** (30 mg) in anhydrous DMF (3 mL) under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-(bis-trifluoromethyl-benzyl)-methylamine hydrochloride (25.5 mg), was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL) and a saturated sodium hydrogen carbonate solution (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (30 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.4.

NMR (d_6 -DMSO – 60°C): δ (ppm) 7.94 (s, 1H); 7.8 (s, 2H); 7.16 (m, 1H); 6.89 (m, 1H); 6.75 (m, 1H); 4.54 (s, 2H); 3.6-3.0 (m, 4H); 2.7 (s, 3H); 2.8-2.4 (m, 4H); 2.44 (s, 3H); 1.98 (m, 1H); 1.74 (m, 2H); 1.49 (m, 1H); 1.3 (bs, 9H).

Intermediate 41

4-[(3,5-Dichlorobenzyl)methylcarbamoyl]-methyl-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

DIPEA (34.3 μ L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (34.3 mg) were added to a solution of intermediate **39** (30 mg) in anhydrous DMF (3 mL) under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-dichlorobenzyl-methylamine hydrochloride (20.5 mg) was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL) and a saturated sodium hydrogen carbonate solution (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (30 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.4.

NMR (d_6 -DMSO): δ (ppm) 7.55-7.45 (m, 1H); 7.25-7.15 (m, 1H); 7.11 (s, 1H); 7.08 (s, 1H); 7.0-6.8 (m, 2H); 4.45-4.3 (m, 2H); 3.6-3.0 (m, 4H); 2.85-2.4 (m, 4H); 2.69 (s, 3H); 2.44 (s, 3H); 2.0-1.8 (m, 1H); 1.72 (m, 2H); 1.5-1.4 (m, 1H); 1.3 (bs, 9H).

Intermediate 42

3-Fluoro-4-oxo-piperidine-1-carboxylate *tert*-butyl ester

Trimethylsilyl trifluoromethanesulfonate (2.17 mL) was added to a solution of *tert*-butyl-4-oxo-1-piperidine carboxylate (2.0 g) and TEA (3.34 mL) in anhydrous DCM (20 mL) previously cooled to -30°C under a Nitrogen atmosphere. The mixture was stirred at this temperature for 1 hour, then it was quickly treated with cold saturated sodium hydrogen carbonate solution (20 mL). The layers were separated and the organic phase was dried and concentrated *in vacuo* to give 1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydro-4-pyridinyl-trifluoromethanesulfonate as a yellow oil, which was dissolved in anhydrous acetonitrile (80

mL) and the resulting solution was treated with Selectfluor (3.89 g). The mixture was stirred at r.t. for 1 hour, then it was concentrated *in vacuo* and the residue was dissolved in AcOEt (50 mL). The organic layer was washed with a saturated sodium hydrogen solution (30 mL), dried and concentrated *in vacuo* to a residue, which was purified by chromatography on neutral Alumina Brochmann type 1 (initially AcOEt then AcOEt/MeOH 95:5) to give the title compound (0.99 g) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.3.

NMR (d₆-DMSO): δ (ppm) 5.08 (dd, 1H); 4.32 (bm, 1H); 4.0 (bm, 1H); 3.19 (m, 2H); 2.56 (m, 1H); 2.36 (m, 1H); 1.43 (s, 9H).

Intermediate 43

5-Ethoxycarbonyl-3-fluoro-4-oxo-azepine-1-carboxylic acid *tert*-butyl ester

Ethyl diazoacetate (7.8 mL) and boron trifluoride diethyl etherate (7.2 mL) were added simultaneously over 50 minutes to a suspension of intermediate 42 (12.39 g) in dry Et₂O (250 mL) previously cooled to -20°C under a Nitrogen atmosphere. The solution obtained was stirred at -20°C for 1 hour, then it was allowed to warm to 0°C, and treated with a saturated potassium carbonate solution (200 mL). The layers were separated and the organic phase was dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 9:1) to give the title compound (5.42 g) as a yellow oil.

T.l.c.: CH/AcOEt 85:15, R_f=0.1 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 5.06 (dt, 1H); 4.3-4.1 (m, 2H); 3.53 (m, 1H); 4.0-3.2 (bs, 4H); 2.2-2.0 (m, 2H); 1.4 (s, 9H); 1.3-1.2 (t, 3H).

MS (ES/+): m/z=304 [MH]⁺.

Intermediate 44

3-Fluoro-4-oxo-azepine-1-carboxylic acid, *tert*-butyl ester

A suspension of intermediate 43 (100 mg) in 3M hydrochloric acid (5 mL) was heated to reflux for 6 hours. The mixture was concentrated *in vacuo* to give the 3-fluoro-azepin-4-one hydrochloride (60.5 mg) as a whitish solid.

Di *tert*-butyl dicarbonate (86 mg) was added to a suspension of this compound (60.5 mg) and TEA (0.1 mL) in anhydrous DCM (5 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight. The mixture was treated with a saturated ammonium chloride solution (10 mL) and extracted with further DCM (2 x 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (50 mg) as a colourless oil.

T.l.c.: CH/AcOEt 7:3, R_f=0.23 (detection with ninhydrine).

NMR (d₆-DMSO - 70°C): δ (ppm) 5.15 (dt, 1H); 3.76 (m, 2H); 3.53 (bm, 1H); 3.23 (bm, 1H); 2.54 (m, 1H); 2.43 (m, 1H); 1.71 (m, 1H); 1.64 (m, 1H); 1.35 (s, 9H).

Intermediate 45**4-(1-Cyano-1-ethoxycarbonyl-methyl)-3-fluoro-azepine-1-carboxylic acid *tert*-butyl ester**

- 5 A round bottom flask equipped with a Dean Stark apparatus was charged with intermediate 44 (1.136 g), ethyl cyanoacetate (0.576 mL), methyl ammonium acetate (0.189 g) and acetic acid (0.281 mL) in anhydrous benzene (9 mL). The mixture was heated to reflux overnight, then it was allowed to cool to r.t. and washed with water (20 mL). The aqueous layer was extracted with AcOEt (2 x 20 mL). The combined organic extracts were washed with 1M sodium hydroxide solution (20 mL) and a saturated ammonium chloride solution (20 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (0.873 g – cis/trans mixture) as a colourless oil. T.l.c.: CH/AcOEt 7:3, R_f=0.28 (detection with ninhydrine). MS (ES/+): m/z= 326 [MH]⁺.
- 15

Intermediate 46**4-(1-Cyano-1-ethoxycarbonyl-methyl)-3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester (anti isomer)**

- 20 A small amount of iodine and 3 drops of methyl iodide were added to a suspension of magnesium turnings (215 mg) in dry Et₂O (5 mL), at r.t., under a Nitrogen atmosphere, then the mixture was vigorously refluxed. 2-Bromo-5-fluoro-toluene (1.016 mL) was added over 1 hour to this mixture followed by further Et₂O (2 mL). The suspension was heated under vigorous reflux for 1 hour. A solution of intermediate 45 (0.873 g) in anhydrous Et₂O (3 mL) was added to the solution of Grignard so obtained over 30 minutes. The resulting mixture was refluxed for further 30 minutes then it was cooled to 0°C, a 3M sulfuric acid solution (3 mL) was added and the aqueous layer was extracted with AcOEt (2 x 30 mL).
- 25 The combined organic layers were washed with a saturated sodium hydrogen carbonate (30 mL) and water (15 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 9:1 to 8:2) to give the title compound (308.4 mg) as a colourless oil.
- 30 T.l.c.: CH/AcOEt 8:2, R_f=0.21 (detection with ninhydrine).
NMR (d₆-DMSO - 70°C): δ (ppm) 7.34-7.27 (2m, 2H); 7.05-6.96 (bm, 2H); 5.8 (2bd, 1H); 4.58-4.33 (2s, 1H); 4.07 (m, 2H); 3.8-3.5 (bm, 2H); 3.4-3.0 (bm, 2H); 2.7-2.3 (bm, 1H); 1.8 (1.6 (bm, 1H); 1.8-1.6 (bm, 1H); 1.5-1.2 (bm, 1H); 1.23 (bs, 9H); 1.13-0.96 (2t, 3H).
- 35 MS (ES/+): m/z= 437 [MH]⁺.

Intermediate 47

4-Carboxymethyl-3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester (anti isomer)

A mixture of intermediate 46 (0.29 g) in acetic acid (3 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C for 6 hours. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (30 mL). Then, di-*tert*-butyl-dicarbonate (145 mg) was added and the resulting mixture was stirred at r.t. overnight. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=1 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt from 8:2 to 6:4) to give the title compound (79.7 mg) as a pale yellow oil.

T.l.c.: CH/AcOEt 7:3, R_f=0.18 (detection with ninhydrine).

NMR (d₆-DMSO - 70°C): δ (ppm) 11.64 (bs, 1H); 7.25 (dd, 1H); 6.96 (dd, 1H); 5.57 (dt, 1H); 3.78 (bm, 2H); 3.18 (bt, 2H); 2.83 (d, 1H); 2.68 (d, 1H); 2.47 (s, 3H); 2.33 (m, 1H); 2.09 (m, 1H); 1.79 (m, 1H); 1.59 (m, 1H); 1.31 (s, 9H).

MS (ES/+): m/z= 384 [MH]⁺.

Intermediate 48

4-{[(3,5-Bis-trifluoromethyl-benzyl)methylcarbamoyl]-methyl}-3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid, *tert*-butyl ester(anti isomer)

DIPEA (50 μ L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (37 mg) were added to a solution of intermediate 47 (34 mg) in anhydrous DMF (5 mL) under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-(bis-trifluoromethyl-benzyl)-methylamine hydrochloride (28.7 mg), was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (37.1 mg) as a colourless oil.

T.l.c.: CH/AcOEt 7:3, R_f=0.19.

NMR (d₆-DMSO): δ (ppm) 8.04-7.88 (2bs, 1H); 7.77-7.72 (2bs, 2H); 7.12 (m, 1H); 6.91 (m, 1H); 6.73 (m, 1H); 5.8-5.62 (2bd, 1H); 4.8-4.4 (m, 2H); 3.9-3.5 (bm, 2H); 3.13 (bm, 2H); 2.92 (bm, 2H); 2.83-2.81 (2bs, 3H); 2.44-2.42 (2bs, 3H); 2.35-2.0 (bm, 2H); 1.67 (bm, 1H); 1.48 (bm, 1H); 1.28 (s, 9H).

Intermediate 49

4-{[(3,5-Dichlorobenzyl)methylcarbamoyl]-methyl}-3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid, *tert*-butyl ester(anti isomer)

DIPEA (50 μ L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (36.2 mg) were added to a solution of intermediate 47 (33.2 mg) in anhydrous DMF (5 mL) under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-dichlorobenzyl-methylamine-

hydrochloride (21.6 mg), was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 75:25) to give the title compound (38.4 mg) as a colourless oil.

5 T.l.c.: CH/AcOEt 7:3, R_f=0.21.

NMR (d₆-DMSO): \square (ppm) 7.49-7.42 (2t, 1H); 7.13 (m, 1H); 7.02 (d, 2H); 6.85 (m, 2H); 5.81-5.65 (2bd, 1H); 4.41-4.28 (2m, 2H); 3.9-3.5 (m, 2H); 3.08 (bm, 2H); 2.86 (m, 2H); 2.72-2.7 (2s, 3H); 2.41-2.4 (2s, 3H); 2.35-2.0 (bm, 2H); 1.65 (bm, 1H); 1.45 (bm, 1H); 1.25 (s, 9H).

10

Intermediate 50

4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of phenyl magnesium bromide (1.0M in THF – 37 mL) was added drop-wise to a mixture of intermediate 1 (6 g) and copper iodide (1.18 g) in anhydrous THF (48 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and stirred at 23°C for 40 minutes. The mixture was cooled to 0°C, treated with 3M hydrochloric acid solution until pH=5 and extracted with AcOEt (3 x 50 mL). The combined organic extracts were washed with a saturated ammonium chloride solution (100 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 85:15) to give the title compound (5.2 g) as a colourless oil.

20

T.l.c.: CH/AcOEt 8:2, R_f=0.24 (detection with ninhydrine).

Intermediate 51

4-Carboxymethyl-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate 50 (5.2 g) in acetic acid (59 mL), conc. sulfuric acid (19.5 mL) and water (19.5 mL) was heated to 140°C for 12 hours. The solution was allowed to cool to r.t., a 2.5M sodium hydroxide solution added, followed by sodium hydroxide pellets until pH 8. Then, di-*tert*-butyl-dicarbonate (5.9 g) was added and the resulting mixture was stirred at r.t. for 2 days. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=6-7 and then extracted with AcOEt (3 x 50 mL). The organic phase was washed with brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (2.15 g) as a white solid.

30

T.l.c.: CH/AcOEt 1:1, R_f=0.18 (detection with ninhydrine).

35 MS (ES/+): m/z= 342 [M+Na]⁺.

Intermediate 52

[1-(3,5-Dichloro-phenyl)-ethyl]-methylamine

Methylamine (2M solution in MeOH – 13 mL) was added to a solution of 3,5-dichloroacetophenone (500 mg) in MeOH (26 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. for 18 hours, then it was cooled to 0°C and sodium borohydride (98 mg) was added. The mixture was stirred at 0°C for 2 hours, then it was quenched with water and extracted with DCM. The organic layer was dried and concentrated *in vacuo* to give the title compound (340 mg) as an yellow oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.15.

NMR (CDCl₃): δ (ppm) 7.3 (m, 3H); 3.6 (q, 1H); 2.3 (s, 3H); 1.35 (d, 3H).

MS (ES/+): m/z=204 [M+H]⁺.

Intermediate 53

[1-(3,5-Dibromo-phenyl)-ethyl]-methylamine

Methylamine (2M solution in MeOH – 138 mL) was added to a solution of 3,5-dibromoacetophenone (7.7 g) in MeOH (138 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight, then it was cooled to 0°C and sodium borohydride (1.57 g) was added. The mixture was allowed to reach r.t. in 3 hours, then it was concentrated *in vacuo*, the residue was dissolved in Et₂O and washed with water and brine. The organic layer was dried and concentrated *in vacuo* to give the title compound (7.8 g) as an orange oil.

T.l.c.: DCM/MeOH 9:1, R_f=0.32.

MS (ES/+): m/z=294 [M+H]⁺.

Intermediate 54 and Intermediate 55

[1-(3,5-Dichloro-phenyl)-ethyl]-methylamine (54, Enantiomer 1) and (55, Enantiomer 2)

To a solution of intermediate 52 (759 mg) in dry THF (4 ml), a solution of di-p-toluoyl-D-tartaric acid (1.3 g) in dry THF (4 ml) was added. The solution was stirred at r. t. overnight. The suspension obtained was filtered and the solid residue washed with dry THF (13 ml). The solid (1.8 g) was crystallised from dry THF (15 ml) by heating to reflux for 1 hour, cooling to r.t. and stirring for 2 hours. The suspension was filtered and the solid residue (1 g) washed with dry THF (15 ml) and recrystallised as described above twice to give [1-(3,5-dichloro-phenyl)-ethyl]-methylamine di-p-toluoyl-D-tartrate salt (690 mg). The solid was stirred in a mixture of saturated sodium hydrogen carbonate solution (20 ml) and DCM (20 ml). The organic phase was washed with water (20 ml), dried and concentrated *in vacuo* to give the title compound intermediate 55 (230 mg) as colourless oil.

The mother liquors from the precipitation and crystallizations were collected, concentrated *in vacuo*, treated with saturated sodium hydrogen carbonate solution (20 ml) and extracted with DCM (20 ml). The colourless oil thus obtained (550 g) was processed with di-p-toluoyl-L-tartaric acid (1.04 g) in dry THF as described above (one precipitation and three recrystallisations) to give [1-(3,5-dichloro-phenyl)-ethyl]-methylamine di-p-toluoyl-L-tartrate

salt (820 mg). The solid was stirred in a mixture of saturated sodium hydrogen carbonate solution (20 ml) and DCM (20 ml). The organic phase was washed with water (20 ml), dried and concentrated *in vacuo* to give the title compound intermediate 54 (238 mg) as colourless oil.

5 **Intermediate 54:**

NMR (CDCl₃): δ (ppm) 7.3 (m, 3H); 3.6 (q, 1H); 2.3 (s, 3H); 1.35 (d, 3H).

MS (ES/+): $m/z=204$ [M+H]⁺.

HPLC (column: Chiral-AGP 15cm x 2mm, 5 μ m; injection volume=1 μ L; mobile phase: ammonium phosphate buffer 100mM pH=4.4 / acetonitrile isocratic 96/4 % v/v; flow rate= 0.13 mL/min; detection: $\lambda=210$ nm): retention time = 5.2 minutes; purity (a/a %) 100%.

Intermediate 55:

NMR (CDCl₃): δ (ppm) 7.3 (m, 3H); 3.6 (q, 1H); 2.3 (s, 3H); 1.35 (d, 3H).

MS (ES/+): $m/z=204$ [M+H]⁺.

HPLC (column: Chiral-AGP 15cm x 2mm, 5 μ m; injection volume=1 μ L; mobile phase: ammonium phosphate buffer 100mM pH=4.4 / acetonitrile isocratic 96/4 % v/v; flow rate= 0.13 mL/min; detection: $\lambda=210$ nm): retention time = 5.5 minutes; purity (a/a %) 98.5%.

Intermediate 56 and Intermediate 57

[1-(3,5-Dibromo-phenyl)-ethyl]-methylamine (56, Enantiomer 1) and (57, Enantiomer 2)

To a solution of intermediate 53 (1.3 g) in dry THF (7 ml), a solution of di-p-toluoyl-D-tartaric acid (1.7 g) in dry THF (7 ml) was added. The solution was stirred at r.t. overnight. The suspension obtained was filtered and the solid residue washed with dry THF (2 x 10ml). The solid obtained (1.2 g) was crystallised from dry THF (15 ml) by heating to reflux for 1 hour, cooling to r.t. and stirring for 2 hours. The suspension was filtered and the solid residue (0.88 g) washed with dry THF (15 ml) and recrystallised as described above twice to give [1-(3,5-dibromo-phenyl)-ethyl]-methylamine di-p-toluoyl-D-tartrate salt (542 mg). The solid was stirred in a mixture of saturated sodium hydrogen carbonate solution (20 ml) and DCM (20ml). The organic phase was washed with water (20 ml), dried and concentrated *in vacuo* to give the title compound intermediate 57 (180mg) as colourless oil.

The two first mother liquors were collected, concentrated *in vacuo* and treated with saturated sodium hydrogen carbonate solution (20 ml) and extracted with DCM (20 ml). The colourless oil thus obtained (880 mg) was processed with di-p-toluoyl-L-tartaric acid (1.16 g) in dry THF as described above (one precipitation and three recrystallisations) to give the [1-(3,5-dibromo-phenyl)-ethyl]-methylamine di-p-toluoyl-L-tartrate salt (603 mg). The solid was stirred in a mixture of saturated sodium hydrogen carbonate solution (20 ml) and DCM (20

ml). The organic phase was washed with water (20 ml), dried and concentrated *in vacuo* to give the title compound intermediate 56 (225 mg) as colourless oil.

Intermediate 56:

NMR (CDCl₃): δ (ppm) 7.6 (t, 1H); 7.4 (d, 2H); 3.6 (q, 1H); 2.3 (s, 3H); 1.3 (d, 3H).

5 MS (ES/+): $m/z=294$ [M+H]⁺.

HPLC (column: Chiral-AGP 15cm x 2mm, 5 μ m; injection volume=1 μ L; mobile phase: ammonium phosphate buffer 100mM pH=4.4 / acetonitrile isocratic 96/4 % v/v; flow rate=0.13 mL/min; detection: $\lambda=210$ nm): retention time = 7.7 minutes; purity (a/a %) 98.2%.

Intermediate 57:

10 NMR (CDCl₃): δ (ppm) 7.6 (t, 1H); 7.4 (d, 2H); 3.6 (q, 1H); 2.3 (s, 3H); 1.3 (d, 3H).

MS (ES/+): $m/z=294$ [M+H]⁺.

HPLC (column: Chiral-AGP 15cm x 2mm, 5 μ m; injection volume=1 μ L; mobile phase: ammonium phosphate buffer 100mM pH=4.4 / acetonitrile isocratic 96/4 % v/v; flow rate=0.13 mL/min; detection: $\lambda=210$ nm): retention time = 9.1 minutes; purity (a/a %) 99.3%.

15

Intermediate 58

4-([(3,5-Dibromobenzyl)methylcarbamoyl]methyl)-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (1.3 mL) and O-(benzotriazol-1-yl)-N,N,N'-tetramethyluronium tetrafluoroborate (1.05g) were added to a solution of intermediate 3 (850 mg) in anhydrous DMF (12 mL) under a Nitrogen atmosphere. After stirring for 15 minutes, 3,5-dibromobenzyl-methylamine hydrochloride (794 mg) was added. The mixture was stirred at r.t. for 48 hours, then it was diluted with DCM and washed with 5% sodium hydrogen carbonate and brine. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt from 7:3 to 1:1) to give the title compound (1.38 g) as a colourless oil.

25 T.l.c.: CH/AcOEt 1:1, R_f=0.35 (detection with ninhydrine).

MS (ES/+): $m/z=621$ [M+Na]⁺.

Intermediate 59

30 4-([1-(3,5-Dichloro-phenyl)-ethylcarbamoyl]-methyl)-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (675 μ L) and O-(benzotriazol-1-yl)-N,N,N'-tetramethyluronium tetrafluoroborate (525 mg) were added to a solution of intermediate 3 (426 mg) in anhydrous DMF (6 mL) under a Nitrogen atmosphere. After stirring for 15 minutes, 1-(3,5-dichloro-phenyl)-ethylamine hydrochloride (283 mg) was added. The mixture was stirred at r.t. for 48 hours,

35 then it was diluted with DCM(14 mL), washed with 5% sodium hydrogen carbonate solution (12 mL), and passed through a phase separation cartridge with polypropylene frit and

concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (343 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, R_f=0.28 (detection with ninhydrine).

MS (ES/+): m/z=531 [M+Na]⁺.

5

Intermediate 60

4-([1-(S)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl)-methyl-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

- 10 DIPEA (675 μ L) and O-(benzotriazol-1-yl)-N,N,N'-tetramethyluronium tetrafluoroborate (525 mg) were added to a solution of intermediate 3 (426 mg) in anhydrous DMF (6 mL) under a Nitrogen atmosphere. After stirring for 15 minutes, [1-(S)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine (341 mg) was added. The mixture was stirred at r.t. for 48 hours, then it was diluted with DCM (14 mL), washed with 5% sodium hydrogen carbonate solution (12 mL), and passed through a phase separation cartridge with polypropylene frit and concentrated *in vacuo*. The residue was purified by SCX cartridge (load with DCM and elution with MeOH, NH₃ 0.2M in MeOH) to give the title compound (590 mg) as a yellow oil.

- 15 T.l.c.: CH/AcOEt 1:1, R_f=0.59 (detection with ninhydrine).
- 20 MS (ES/+): m/z 613 [M+Na]⁺.

Intermediate 61

4-([1-(3,5-Dibromo-phenyl)-ethyl]-methyl-carbamoyl)-methyl-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

- 25 DIPEA (675 μ L) and O-(benzotriazol-1-yl)-N,N,N'-tetramethyluronium tetrafluoroborate (525 mg) were added to a solution of intermediate 3 (426 mg) in anhydrous DMF (6 mL) under a Nitrogen atmosphere. After stirring for 15 minutes, intermediate 53 (369 mg) was added. The mixture was stirred at r.t. for 48 hours, then it was diluted with DCM (14 mL), washed with 5% sodium hydrogen carbonate solution (12 mL), and passed through a phase separation cartridge with polypropylene frit and concentrated *in vacuo*. The residue was purified by SCX Cartridge (load with DCM and elution with MeOH, NH₃ 0.2M in MeOH) to give the title compound (390 mg) as a yellow oil.

- 30 T.l.c.: CH/AcOEt 6:4, R_f=0.3 (detection with ninhydrine).
- MS (ES/+): m/z=635 [M+Na]⁺.

35

Intermediate 62

4-([1-(3,5-Dibromo-phenyl)-ethyl]-methyl-carbamoyl)-methyl-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (enantiomer 1)

DIPEA (236 \square L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (285 mg) were added to a solution of intermediate 3 (230 mg) in anhydrous DMF (5 mL) under a Nitrogen atmosphere. After stirring for 30 minutes intermediate 56 (220 mg) was added. The mixture was stirred at r.t. overnight, then it was taken up with AcOEt (30 mL) and washed with water (4 x 30 mL) and brine (2 x 10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 9/1 then CH/AcOEt 8/2) to give the title compound (380 mg) as a white foam.

T.l.c.: CH/AcOEt 6:4, R_f=0.3 (detection with ninhydrine).

MS (ES/+): m/z=635 [M+Na]⁺.

Intermediate 63

4-([1-(3,5-Dibromo-phenyl)-ethyl]-methyl-carbamoyl)-methyl-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (enantiomer 2)

DIPEA (195 \square L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (232 mg) were added to a solution of intermediate 3 (188 mg) in anhydrous DMF (5 mL) under a Nitrogen atmosphere. After stirring for 30 minutes intermediate 57 (180 mg) was added. The mixture was stirred at r.t. overnight, then it was taken up with AcOEt (30 mL) and washed with water (4 x 5 mL) and brine (2 x 5 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7/3) to give the title compound (320 mg) as a white foam.

T.l.c.: CH/AcOEt 6:4, R_f=0.3 (detection with ninhydrine).

MS (ES/+): m/z=635 [M+Na]⁺.

Intermediate 64

4-([1-(3,5-Dichloro-phenyl)-ethyl]-methyl-carbamoyl)-methyl-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (enantiomer 1)

DIPEA (206 \square L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (248 mg) were added to a solution of intermediate 3 (200 mg) in anhydrous DMF (5 mL) under a Nitrogen atmosphere. After stirring for 30 minutes intermediate 54 (124 mg) was added. The mixture was stirred at r.t. overnight, then it was taken up with AcOEt (30 mL) and washed with water (3 x 30 mL) and brine (2 x 10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 9/1 then CH/AcOEt 8/2) to give the title compound (290 mg) as a white foam.

T.l.c.: CH/AcOEt 6:4, R_f=0.27 (detection with ninhydrine).

MS (ES/+): m/z=545 [M+Na]⁺.

Intermediate 65**4-([(3,5-Dibromobenzyl)methylcarbamoyl]methyl)-4-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester**

DIPEA (0.5 mL) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (392 mg) were added to a solution of intermediate 51 (300 mg) in anhydrous DMF (4.5 mL) under a Nitrogen atmosphere. After stirring for 30 minutes 3,5-dibromobenzyl-methylamine hydrochloride (296 mg) was added. The mixture was stirred at r.t. 30 hours, then it was diluted with DCM (12 mL) and saturated sodium hydrogen carbonate solution (14 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by SCX cartridge (load with MeOH/DCM 1:1 and elution with NH₃ 0.2M in MeOH) to give the title compound (521 mg) as a yellow oil.

T.l.c.: CH/AcOEt 8:2, R_f=0.14 (detection with ninhydrine).

MS (ES/+): m/z=603 [M+Na]⁺.

Intermediate 66**4-([(1-(S)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl)-methyl-carbamoyl]-methyl)-4-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester**

DIPEA (0.5 mL) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (392 mg) were added to a solution of intermediate 51 (300 mg) in anhydrous DMF (4.5 mL) under a Nitrogen atmosphere. After stirring for 30 minutes [1-(S)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine (255 mg) was added. The mixture was stirred at r.t. 30 hours, then it was diluted with DCM (12 mL) and saturated sodium hydrogen carbonate solution (14 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by SCX cartridge (load with MeOH/DCM 1:1 and elution with NH₃ 0.2M in MeOH) to give the title compound (465 mg) as a yellow oil.

T.l.c.: CH/AcOEt 8:2, R_f=0.12 (detection with ninhydrine).

MS (ES/+): m/z= 595 [M+Na]⁺.

Intermediate 67**4-([(1-(3,5-Dibromo-phenyl)-ethyl)-methyl-carbamoyl]-methyl)-4-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester**

DIPEA (100 μ L) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (78.5 mg) were added to a solution of intermediate 51 (60 mg) in anhydrous DMF (0.9 mL) under a Nitrogen atmosphere. After stirring for 30 minutes, intermediate 53 (55 mg) was added. The mixture was stirred at r.t. 30 hours, then it was diluted with DCM (12 mL) and saturated sodium hydrogen carbonate solution (14 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by SCX cartridge (load with MeOH/DCM

1:1 and elution with NH_3 0.2M in MeOH) to give the title compound (107 mg) as a yellow oil.

T.l.c.: CH/AcOEt 8:2, $R_f=0.17$ (detection with ninhydrine).

5 Intermediate 68

4-([1-(3,5-Dibromo-phenyl)-ethyl]-methyl-carbamoyl)-methyl-4-phenyl-piperidine-1-carboxylic acid tert-butyl ester (enantiomer 1)

10 DIPEA (200 μL) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (234 mg) were added to a solution of intermediate 51 (180 mg) in anhydrous DMF (8 mL) under a Nitrogen atmosphere. After stirring for 30 minutes intermediate 56 (182 mg) was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt and washed with ice/water and brine. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt from 8:2 to 6:4) to give the title compound
15 (320 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, $R_f=0.53$ (detection with ninhydrine).

MS (ES/+): $m/z=617$ $[\text{M}+\text{Na}]^+$.

20 Intermediate 69

4-([1-(3,5-Dichloro-phenyl)-ethyl]-methyl-carbamoyl)-methyl-4-(4-fluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester

Intermediate 59 (493 mg) was dissolved in dry THF (15 mL) under a Nitrogen atmosphere and NaH (60% suspension in mineral oil, 116 mg) was added in small portions. The reaction
25 mixture was stirred under these conditions for 10 minutes then methyl iodide (363 μL) was added, and the reaction was heated up to 50°C and kept at this temperature for 7 hours. Then it was diluted with AcOEt (15 x 2 mL), washed with water (15 mL), and the dried organic phase was concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 8:2 to 1:1) to give the title compound (300 mg) as a white solid.

30 T.l.c.: CH/AcOEt 1:1, $R_f=0.43$ (detection with ninhydrine).

MS (ES/+): $m/z=523$ $[\text{M}+\text{H}]^+$.

Example 1

35 N-(3,5-Dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide hydrochloride

TFA (0.5 mL) was added to a solution of intermediate 4 (80 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 1:1 containing 0.5% of conc. ammonium hydroxide solution) to give the N-(3,5-dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide (40 mg) as a pale yellow oil (T.l.c.: AcOEt/MeOH 1:1 containing 0.5% of conc. NH₄OH, R_f=0.03).

This compound (40 mg) was dissolved in anhydrous Et₂O (1 mL) and treated with hydrochloric acid (1M in Et₂O – 0.195 mL) at 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound (40 mg) as a white solid.

NMR (d₆-DMSO – 70°C): δ (ppm) 8.48 (bs, 2H); 7.52-7.47 (2bs, 1H); 7.41 (m, 2H); 7.15-7.11 (2t, 2H); 7.02-7.0 (2s, 2H); 4.29-4.19 (s, 2H); 3.21 (m, 2H); 2.88 (m, 2H); 2.79-2.75 (2s, 3H); 2.54 (s, 3H); 2.4-2.2 (m, 4H).

Example 2

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide hydrochloride (anti isomer)

TFA (0.5 mL) was added to a solution of intermediate 9 (60 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 8:2) to give the N-(3,5-dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide (45 mg) as a pale yellow oil (T.l.c.: AcOEt/MeOH 8:2, R_f=0.1).

This compound was dissolved in anhydrous Et₂O (1 mL) and treated with hydrochloric acid (1M in Et₂O – 0.21 mL) at 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound (42 mg) as a white solid.

NMR (d₆-DMSO – 70°C): δ (ppm) 8.95 (bs, 2H); 7.46 (m, 2H); 7.39 (bs, 1H); 7.13 (t, 2H); -6.99 (bs, 2H); 5.86 (bd, 1H); 4.3 (m, 2H); 3.48 (m, 1H); 3.18 (m, 1H); 2.99 (m, 1H); 2.94 (d, 1H); 2.76 (d, 1H); 2.75 (m, 1H); 2.69 (m, 1H); 2.66 (s, 3H); 2.27 (bm, 1H).

Example 3

4-(4-Fluorophenyl)-piperidine-4-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride

Hydrochloric acid (4M in dioxan – 0.21 mL) was added to a solution of intermediate 17 (35 mg) in anhydrous DCM (2 mL) previously cooled to -5°C under a Nitrogen atmosphere. The solution was allowed to warm to r.t. and stirred at r.t. for 30 hours, then it was concentrated *in vacuo* and the residue was purified by flash chromatography (from CH₂Cl₂/AcOEt 6:4 to MeOH) to give 4-(4-fluorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide (18 mg).

This material was dissolved in Et₂O (1 mL), cooled to -0°C and treated with hydrochloric acid (4M in Et₂O – 72 μ L). The mixture was stirred at 0°C for 10 minutes, then it was concentrated *in vacuo* to give the title compound (18 mg) as a white solid.

NMR (d₆-DMSO – 70°C): δ (ppm) 8.66 (bm, 2H); 7.94 (bs, 1H); 7.72 (bs, 2H); 7.32 (dd, 2H); 7.17 (t, 2H); 4.65 (s, 2H); 3.28 (m, 2H); 3.1 (m, 2H); 2.62 (s, 3H); 2.52 (m, 2H); 2.14 (m, 2H).

MS (ES/+): m/z=463 [MH-HCl]⁺.

Example 4

4-(4-Chlorophenyl)-piperidine-4-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride

Hydrochloric acid (4M in dioxan – 86 μ L) was added to a solution of intermediate 22 (15 mg) in anhydrous DCM (0.2 mL) previously cooled to -5°C under a Nitrogen atmosphere.

The solution was allowed to warm to r.t. and stirred at r.t. for 30 hours, then it was concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 7:3) to give 4-(4-chlorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide (11 mg).

This material was dissolved in Et₂O (1 mL), cooled to -0°C and treated with hydrochloric acid (4M in Et₂O – 54 μ L). The mixture was stirred at 0°C for 10 minutes, then it was concentrated *in vacuo* to give the title compound (10.3 mg) as a beige solid.

NMR (d₆-DMSO – 70°C): δ (ppm) 8.8 (bm, 1H); 7.92 (s, 1H); 7.71 (s, 2H); 7.39 (d, 2H); 7.28 (d, 2H); 4.63 (s, 2H); 3.26 (m, 2H); 3.0 (m, 2H); 2.61 (s, 3H); 2.5 (m, 2H); 2.15 (m, 2H).

MS (ES/+): m/z=479 [MH-HCl]⁺.

Example 5

4-(4-Fluorophenyl)-piperidine-4-carboxylic acid (3,5-dichloro-benzyl)-methylamide hydrochloride

TFA (3.2 mL) was added to a solution of intermediate 23 (80 mg) in anhydrous DCM (13 mL) previously cooled to -0°C under a Nitrogen atmosphere. The solution was stirred at -0°C for 18 hours, then it was concentrated *in vacuo*. The residue was dissolved in AcOEt (30 mL) and washed with saturated sodium carbonate solution (20mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (first

AcOEt then MeOH) to give 4-(4-fluorophenyl)-piperidine-4-carboxylic acid (3,5-dichlorobenzyl)-methylamide (27 mg).

This material was dissolved in Et₂O (2 mL), cooled to -0°C and treated with hydrochloric acid (4M in Et₂O – 140 \square L). The mixture was stirred at 0°C for 10 minutes, then it was concentrated *in vacuo* to give the title compound (22.5 mg) as a beige solid.

NMR (d₆-DMSO – 70°C): \square (ppm) 8.66 (bs, 2H); 7.44 (t, 1H); 7.33 (dd, 2H); 7.29 (t, 2H); 7.1 (s, 2H); 4.46 (s, 2H); 3.27 (m, 2H); 3.1 (m, 2H); 2.58 (s, 3H); 2.5 (m, 2H); 2.13 (t, 2H).

MS (ES/+): m/z=395 [MH-HCl]⁺.

10 Example 6

N-(3,5-Bis-trifluoromethyl)-benzyl-2-[(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide

TFA (1.9 mL) was added to a solution of intermediate 30 (144 mg) in anhydrous DCM (2.5 mL) under a Nitrogen atmosphere. The solution was stirred at 23°C for 3 hours, then it was diluted with DCM and washed with saturated potassium carbonate solution and brine. The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (from AcOEt/MeOH 1:1 to AcOEt/MeOH 3:7 + 3% NH₄OH, then MeOH + 4% NH₄OH) to give the title compound (94 mg) as colourless oil.

T.l.c.: AcOEt/MeOH 1:1 + 1%NH₄OH, R_f=0.08 (detection with ninhydrine).

NMR (d₆-DMSO): \square (ppm) 7.98 (bs, 1H); 7.74 (bs, 2H); 7.17 (dd, 1H); 6.84 (dd, 1H); 6.7 (dt, 1H); 4.46 (s, 2H); 2.83 (s, 2H); 2.79 (bt, 2H); 2.62 (s, 3H); 2.56 (bt, 2H); 2.41 (s, 3H); 2.15 (m, 2H); 1.97 (m, 2H).

MS (ES/+): m/z=491 [M+H]⁺.

25 Example 7

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide

TFA (0.4 mL) was added to a solution of intermediate 29 (30 mg) in anhydrous DCM (0.5 mL) under a Nitrogen atmosphere. The solution was stirred at 23°C for 1 hour, then it was diluted with DCM and washed with saturated potassium carbonate solution and brine. The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (from AcOEt/MeOH 1:1 to AcOEt/MeOH 3:7 + 3% NH₄OH) to give the title compound (23.5 mg) as colourless oil.

T.l.c.: AcOEt/MeOH 3:7 + 3%NH₄OH, R_f=0.12 (detection with ninhydrine).

NMR (d₆-DMSO): \square (ppm) 7.45 (s, 1H); 7.25 (dd, 1H); 7.02 (s, 2H); 7.0-6.8 (m, 2H); 4.28 (s, 2H); 2.81-2.78 (s + m, 4H); 2.55-2.57 (m, 5H); 2.43 (s, 3H); 2.17 (m, 2H); 1.99 (m, 2H).

MS (ES/+): m/z=423 [M+H]⁺.

Example 8**N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide hydrochloride**

The compound of Example 7 (19 mg) was dissolved in Et₂O (0.2 mL), cooled to 0°C and treated with hydrochloric acid (1M in Et₂O – 54 μ L). The mixture was stirred at 0°C for 10 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane to give the title compound (19.3 mg) as a white solid.

NMR (d₆-DMSO): δ (ppm) 8.46 (bd, 2H); 7.4 (s, 1H); 7.3 (m, 1H); 7.02 (s, 2H); 6.94 (m, 2H); 4.31 (s, 2H); 3.23-2.9 (m, 4H); 2.88 (m, 2H); 2.63 (s, 3H); 2.5 (s, 3); 2.5-2.3 (m, 4H).

Example 9**N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluorophenyl)-azepin-4-yl]-N-methyl-acetamide hydrochloride**

TFA (0.5 mL) was added to a solution of intermediate 37 (16 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM/MeOH 8:2) to give N-(3,5-bis-trifluoromethyl-benzyl)-2-[4-(4-fluorophenyl)-azepin-4-yl]-N-methyl-acetamide (12 mg - T.l.c.: DCM/MeOH 8:2 + 0.5% NH₄OH, R_f=0.4).

This compound (12 mg) was dissolved in anhydrous Et₂O (1 mL) and treated with hydrochloric acid (1M in Et₂O – 0.05 mL) at 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound (10 mg) as a white solid.

NMR (d₆-DMSO): δ (ppm) 8.41 (bs, 2H); 7.92 (s, 1H); 7.74 (s, 2H); 7.33 (dd, 2H); 7.01 (bt, 2H); 4.5 (m, 2H); 3.27 (dd, 1H); 3.07 (m, 2H); 2.91 (dd, 1H); 2.72 (bs, 3H); 2.81-2.65 (m, 2H); 2.56 (m, 1H); 2.42-2.29 (m, 2H); 2.05 (dd, 1H); 1.86 (bm, 1H); 1.6 (bm, 1H).

Example 10**N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide**

TFA (0.5 mL) was added to a solution of intermediate 40 (30 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM/MeOH 8:2) to give the title compound (17 mg) as a pale yellow oil.

T.l.c.: DCM/MeOH 8:2, R_f=0.5.

NMR (d_6 -DMSO): δ (ppm) 8.06-8.0 (2bs, 1H); 7.8-7.76 (2bs, 2H); 7.23-7.15 (2m, 1H); 6.91 (m, 1H); 6.76 (m, 1H); 4.69 (bs, 1H); 4.53 (m, 1H); 3.0-2.3 (m, 11H); 2.43 (s, 3H); 2.01 (m, 2H); 1.66 (m, 1H); 1.41 (m, 1H).

5 **Example 11**

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide

10 TFA (0.5 mL) was added to a solution of intermediate 41 (30 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM/MeOH 8:2) to give the title compound (20 mg) as a pale yellow oil.

T.l.c.: DCM/MeOH 8:2, Rf=0.5.

15 NMR (d_6 -DMSO): δ (ppm) 7.53-7.47 (2t, 1H); 7.24-7.2 (2dd, 1H); 7.1 (d, 2H); 6.88 (m, 2H); 4.46-4.34 (s + m, 2H); 3.0-2.3 (m, 11H); 2.44 (s, 3H); 2.01 (m, 2H); 1.67 (bm, 1H); 1.39 (bm, 1H).

Example 12

20 **N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide (anti isomer)**

TFA (0.5 mL) was added to a solution of intermediate 48 (35 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (4 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 8:2) to give the title compound (25.1 mg) as a pale yellow oil.

T.l.c.: AcOEt/MeOH 8:2, Rf=0.14.

30 NMR (d_6 -DMSO): δ (ppm) 8.06-7.97 (2bs, 1H); 7.76 (bs, 2H); 7.17-7.13 (2dd, 1H); 6.89 (dd, 1H); 6.78 (dt, 1H); 5.53-5.4 (2bd, 1H); 4.76-4.53 (2m, 2H); 3.25-2.85 (m, 4H); 2.68 (m, 2H); 2.91-2.72 (2s, 3H); 2.44-2.28 (2s, 3H); 2.2 (m, 2H); 1.57 (bm, 1H); 1.3 (bm, 1H).

Example 13

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide (anti isomer)

35 TFA (0.5 mL) was added to a solution of intermediate 49 (36.1 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (4 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the

residue was purified by flash chromatography (AcOEt/MeOH 8:2) to give the title compound (20.5 mg) as a pale yellow oil.

T.l.c.: AcOEt/MeOH 8:2, R_f=0.08.

NMR (d₆-DMSO): δ (ppm) 7.54-7.46 (2t, 1H); 7.16 (m, 1H); 7.11-7.07 (2d, 2H); 6.94 (dd, 1H); 6.87 (m, 1H); 5.6-5.49 (2bd, 1H); 4.55-4.35 (2m, 2H); 3.25-2.88 (m, 2H); 3.05 (m, 2H); 2.85-2.69 (2s, 3H); 2.7 (m, 1H); 2.65-2.35 (m, 1H); 2.46 (2s, 3H); 2.35-2.1 (m, 2H); 1.62-1.5 (2bm, 1H); 1.33-1.23 (bm, 1H).

Example 14

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide (14a enantiomer1) and (14b enantiomer2)

The compound of example 13 (16 mg) was separated into the enantiomers via preparative HPLC (Column: Chiralpack AD 25 x 2 cm; mobile phase: n-hexane/EtOH 8:2; flux=7.5 mL/min; λ 225 nm). Thus, example 14a (6 mg) and example 14b (5.8 mg) were obtained.

Example 14a:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm x 5 μ m, mobile phase n-hexane/EtOH 8:2, flux=1 mL/min, λ 225 nm; retention time 12.2 minutes. Ratio 14a/14b=100:0.

Example 14b:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm x 5 μ m, mobile phase n-hexane/EtOH 8:2, flux=1 mL/min, λ 225 nm; retention time 14.05 minutes. Ratio 14a/14b=0:100.

Example 15

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide (15a enantiomer 1) and (15b enantiomer 2)

The compound of example 12 (21 mg) was separated into the enantiomers via preparative HPLC (Column: Chiralpack AD 25 x 2 cm; mobile phase: n-hexane/EtOH 92:8; flux=7.5 mL/min; λ 225 nm). Thus, example 15a (4.9 mg) and example 15b (6.6 mg) were obtained.

Example 15a:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm x 5 μ m, mobile phase n-hexane/EtOH 85:15, flux=1 mL/min, λ 225 nm; retention time 7.37 minutes. Ratio 15a/15b=96:4.

Example 15b:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm x 5 μ m, mobile phase n-hexane/EtOH 92:8, flux=1 mL/min, λ 225 nm; retention time 8.04 minutes. Ratio 15a/15b=2:98.

Example 16

N-(3,5-Dibromobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide

TFA (12 mL) was added to a solution of intermediate 58 (1.38 g) in DCM (48 mL) previously cooled to 0°C under a Nitrogen atmosphere. The resulting solution was stirred in these

conditions for 1 hour, then a 10% sodium hydroxide solution was added until pH=12. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 9:1 to 7:3 containing 0.5% of conc. NH₄OH) to give the title compound (800 mg) as a white foam.

T.l.c.: DCM/MeOH 8:2 containing 0.5% of conc. NH₄OH, R_f=0.07.

NMR (d₆-acetone): δ (ppm) 7.52 (s, 1H); 7.29 (dd, 2H); 7.21 (s, 2H); 6.89 (t, 2H); 4.24 (s, 2H); 2.77 (dd, 2H); 2.64-2.54 (m, 4H); 2.08-1.9 (mm, 4H); 2.62 (s, 3H).

MS (ES/+): m/z=499 [M+H]⁺.

Example 17

N-(3,5-Dibromo-benzyl)-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide

Sodium triacethoxyborohydride (966 mg) was added to a solution of Example 16 (760 mg) in anhydrous CH₃CN (30 mL) with formaldehyde in water (37% w/w, 460 μ L) under a Nitrogen atmosphere. The mixture was stirred at r.t. for 2 hours, then the solvent was removed *in vacuo* and the residue was dissolved in 5% sodium hydrogen carbonate solution (10 mL) and extracted with DCM (2 x 15 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM, DCM/MeOH from 9:1 to 1:1) to give the title compound (512 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2 containing 0.5% of conc. NH₄OH, R_f=0.62 (detection with ninhydrine).

MS (ES/+): m/z=513 [M+H]⁺.

Example 18

N-(3,5-Dibromo-benzyl)-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide hydrochloride

The compound of Example 17 (512 mg) was dissolved in Et₂O (15 mL), cooled to 0°C and treated with hydrochloric acid (1M in Et₂O – 1.1 mL). The mixture was stirred at 0°C for 30 minutes, then it was filtered under N₂ atmosphere and the precipitate was triturated with pentane to give the title compound (360 mg) as a white solid.

NMR (d₆-DMSO): δ (ppm) 10.0-9.6 (m, 1H); 7.70 (s, 1H); 7.43 (7.36) (dd, 2H); 7.24 (7.21) (s, 2H); 7.18-7.06 (m (t), 2H); 4.27 (s, 2H); 3.38 (s, 3H); 3.31 (m, 2H); 2.79 (q, 2H); 2.62 (bs, 4H); 2.53 (s, 3); 2.05-1.90 (t/t, 1/1H).

Example 19

N-(3,5-Dibromobenzyl)-2-(4-phenyl-piperidin-4-yl)-N-methyl-acetamide TFA (6 mL) was added to a solution of intermediate 65 (518 mg) in anhydrous DCM (24 mL) under a Nitrogen

atmosphere. The solution was cooled at -4°C overnight, then it was treated with 10% sodium hydroxide solution until pH= 8-9 and extracted with DCM. The organic layer was dried and concentrated *in vacuo* to give the title compound (335 mg) as colourless oil.

T.l.c.: DCM/MeOH 8:2, containing 2.5% of conc. NH₄OH, R_f=0.39 (detection with ninhydrine).

MS (ES/+): m/z= 481 [M+H]⁺.

Example 20

N-(3,5-Dibromo-benzyl)-2-(4-phenyl-1-methyl-piperidin-4-yl)-N-methyl-acetamide

Sodium triacethoxyborohydride (99 mg) was added to a solution of Example 19 (100 mg) in anhydrous CH₃CN (5.6 mL) with formaldehyde in water (37% w/w, 47 µL) under a Nitrogen atmosphere. The mixture was stirred at r.t. 3.5 hours, then it was diluted with water (5 mL), AcOEt (10 mL) and washed with brine (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM, DCM/MeOH from 9:1 to 1:1) to give the title compound (93.5 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2, R_f=0.12 (detection with ninhydrine).

NMR (d₆-DMSO): δ (ppm) 7.70 (s, 1H); 7.314-7.10 (m, 7H); 4.28 (s, 2H); 2.63 (s, 3H); 2.5-2.1 (m, 8H); 2.33 (s, 2H); 2.07 (s, 3H).

Example 21

N-[1-(3,5-Dichloro-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-piperidin-4-yl]-N-methyl-acetamide

TFA (3 mL) was added to a solution of intermediate 69 (300 mg) in DCM (12 mL) previously cooled to 0°C under a Nitrogen atmosphere. The resulting solution was stirred in these conditions for 2 hours, then a 10% sodium hydroxide solution was added until pH=12. The aqueous layer was extracted with DCM (2 x 15 mL) which was passed through a phase separation cartridge with polypropylene frit and concentrated *in vacuo*. The residue was purified by SCX cartridge (load with DCM and elution with MeOH, NH₃ 0.2M in MeOH) to give the title compound (118 mg) as a white foam.

T.l.c.: DCM/MeOH 8:2 containing 1% of conc. NH₄OH, R_f=0.07.

MS (ES/+): m/z=423 [M+H]⁺.

Example 22

N-[1-(3,5-Dichloro-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide

Sodium triacethoxyborohydride (126 mg) was added to a solution of Example 21 (100 mg) in anhydrous CH₃CN (5 mL) with a solution of formaldehyde in water (37% w/w, 60 µL) under

a Nitrogen atmosphere. The mixture was stirred at r.t. for 2 hours, then the solvent was removed *in vacuo* and the residue was dissolved in 5% sodium hydrogen carbonate solution (5 ml) and extracted with DCM (2 x 8 mL), which was passed through a phase separation cartridge with polypropylene frit and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM, DCM/MeOH from 95:5 to 1:1) to give the title compound (68 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2 containing 1% of conc. NH₄OH, R_f=0.38 (detection with ninhydrine).

MS (ES/+): m/z=437 [M+H]⁺.

NMR (d₆-DMSO): \square (ppm) 7.24 (dd, 2H); 7.16 (t(s), 1H); 6.93 (t, 2H); 6.87 (s, 2H); 5.77 (q, 1H); 2.58-2.02 (m, 10H); 2.17 (s, 3H); 2.02 (s, 3H); 1.14 (d, 3H).

Example 23

N-[1-(S)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-piperidin-4-yl]-N-methyl-acetamide

TFA (6 mL) was added to a solution of intermediate 60 (590 mg) in DCM (24 mL) previously cooled to 0°C under a Nitrogen atmosphere. The resulting solution was stirred in these conditions for 2 hours, then a 10% sodium hydroxide solution was added until pH=12. The aqueous layer was extracted with DCM (2 x 15 mL) which was passed through a phase separation cartridge with polypropylene frit and concentrated *in vacuo*. The residue was purified by SCX Cartridge (load with DCM and elution with MeOH, NH₃ 0.2M in MeOH) to give the title compound (517 mg) as a white foam.

T.l.c.: DCM/MeOH 8:2 containing 0.5% of conc. NH₄OH, R_f=0.15.

MS (ES/+): m/z=491 [M+H]⁺.

Example 24

N-[1-(S)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide

Sodium triacethoxyborohydride (126 mg) was added to a solution of Example 23 (100 mg) in anhydrous CH₃CN (5 mL) with a solution of formaldehyde in water (37% w/w, 60 μ L) under a Nitrogen atmosphere. The mixture was stirred at r.t. for 2 hours, then the solvent was removed *in vacuo* and the residue was dissolved in 5% sodium hydrogen carbonate solution (5 ml) and extracted with DCM (2 x 8 mL), which was passed through a phase separation cartridge with polypropylene frit and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM, DCM/MeOH from 95:5 to 1:1) to give the title compound (59 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2 containing 0.5% of conc. NH₄OH, R_f=0.42 (detection with ninhydrine).

MS (ES/+): m/z=505 [M+H]⁺.

NMR (d₆-DMSO): δ (ppm) 7.97 (s, 1H); 7.67 (s, 2H); 7.30 (dd, 2H); 7.94 (t, 2H); 5.70 (q,

5 1H); 2.62-2.03 (m, 10H); 2.34 (s, 3H); 2.05 (s, 3H); 1.26 (d, 3H).

Example 25

N-[1-(S)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide hydrochloride —

10

The compound of Example 24 (20 mg) was dissolved in Et₂O (1 mL), cooled to 0°C and treated with hydrochloric acid (1M in Et₂O – 44 μ L). The mixture was stirred at 0°C for 30 minutes, then the solvent was removed *in vacuo* and the residue was triturated with pentane to give the title compound (20 mg) as a white solid.

15 MS (ES/+): m/z=505 [MH-HCl]⁺.

Example 26

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-piperidin-4-yl]-N-methyl-acetamide

20

TFA (6 mL) was added to a solution of intermediate 61 (390 mg) in DCM (24 mL) previously cooled to 0°C under a Nitrogen atmosphere. The resulting solution was stirred in these conditions for 2 hours, then a 10% sodium hydroxide solution was added until pH=12. The aqueous layer was extracted with DCM (2 x 15 mL) which was passed through a phase separation cartridge with polypropylene frit and concentrated *in vacuo*. The residue was

25

purified by SCX cartridge (load with DCM and elution with MeOH, NH₃ 0.2M in MeOH) to give the title compound (290 mg) as a white foam.

T.l.c.: DCM/MeOH 8:2 containing 1% of conc. NH₄OH, R_f=0.15.

MS (ES/+): m/z=513 [M+H]⁺.

30

Example 27

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide

35

Sodium triacethoxyborohydride (126 mg) was added to a solution of Example 26 (100 mg) in anhydrous CH₃CN (5 mL) with a solution of formaldehyde in water (37% w/w, 60 μ L) under a Nitrogen atmosphere. The mixture was stirred at r.t. for 2 hours, then the solvent was removed *in vacuo* and the residue was dissolved in 5% sodium hydrogencarbonate solution (5 ml) and extracted with DCM (2 x 8 mL), which was passed through a phase separation cartridge with polypropylene frit and concentrated *in vacuo*. The residue was purified by flash

chromatography (DCM, DCM/MeOH from 95:5 to 1:1) to give the title compound (46 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2 containing 1% of conc. NH₄OH, R_f=0.65 (detection with ninhydrine).

5 MS (ES/+): m/z=527 [M+H]⁺.

NMR (CDCl₃): δ (ppm) 7.53 (t (s), 1H); 7.31 (dd, 2H); 7.15 (s, 2H); 7.00 (t, 2H); 5.84 (q, 1H); 2.64-2.07 (m, 10H); 2.24 (s, 3H); 2.07 (s, 3H); 1.19 (d, 3H).

Example 28

10 N-[1-(S)-1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-2-(4-phenyl-piperidin-4-yl)-N-methyl-acetamide _

TFA (6 mL) was added to a solution of intermediate 66 (463 mg) in anhydrous DCM (24 mL) under a Nitrogen atmosphere. The solution was cooled at -4°C and kept at this temperature overnight, then it was treated with 10% sodium hydroxide solution until pH= 8-9 and extracted with DCM. The organic layer was dried and concentrated *in vacuo* to give the title compound (348.2 mg) as colourless oil.

15 T.l.c.: DCM/MeOH 8:2 containing 2.5% of conc. NH₄OH, R_f=0.39 (detection with ninhydrine).

20 MS (ES/+): m/z= 473 [M+H]⁺.

Example 29

N-[1-(S)-1-(3,5- Bis-trifluoromethyl-phenyl)-ethyl]-2-(4-phenyl-1-methyl-piperidin-4-yl)-N-methyl-acetamide

25

Sodium triacethoxyborohydride (152 mg) was added to a solution of Example 28 (100 mg) in anhydrous CH₃CN (5.7 mL) with a solution of formaldehyde in water (37% w/w, 70 μ L) under a Nitrogen atmosphere. The mixture was stirred at r.t. 5 hours, then it was diluted with water (5 mL) and washed with 5% sodium hydrogen carbonate solution (10ml) and extracted with DCM. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM, DCM/MeOH from 9:1 to 6:4) to give the title compound (82.8 mg) as a white solid.

30 T.l.c.: DCM/MeOH 8:2, R_f=0.17 (detection with ninhydrine).

35 NMR (CDCl₃): δ (ppm) 7.74 (s, 1H); 7.54 (s, 2H); 7.32-7.10 (m, 5H); 5.98 (q, 1H); 2.70-2.10 (m, 10H); 2.23 (s, 3H); 1.99 (s, 3H); 1.26 (d, 3H).

Example 30

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-(4-phenyl-piperidin-4-yl)-N-methyl-acetamide TFA (2.5 mL) was added to a solution of intermediate 67 (105 mg) in anhydrous DCM (10 mL) under a Nitrogen atmosphere. The solution was cooled at -4°C and kept at this temperature overnight, then it was treated with 10% sodium hydroxide solution until pH= 8-9 and extracted with DCM. The organic layer was dried and concentrated *in vacuo* to give the title compound (78.8 mg) as colourless oil.

T.l.c.: DCM/MeOH 8:2 containing 2.5% of conc. NH₄OH: R_f=0.39 (detection with ninhydrine).

MS (ES/+): m/z= 495 [M+H]⁺.

Example 31

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-(4-phenyl-1-methyl-piperidin-4-yl)-N-methyl-acetamide

Sodium triacethoxyborohydride (102 mg) was added to a solution of Example 30 (70 mg) in anhydrous CH₃CN (3.8 mL) with a solution of formaldehyde in water (37% w/w, 48 µL) under a Nitrogen atmosphere. The mixture was stirred at r.t. 5 hours, then it was diluted with water (5 mL) and washed with 5% sodium hydrogen carbonate solution (10 ml) and extracted with DCM. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM, DCM/MeOH from 9:1 to 6:4) to give the title compound (60.1 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2, R_f=0.12 (detection with ninhydrine).

NMR (CDCl₃): δ (ppm) 7.51 (s, 1H); 7.36-7.18 (m, 5H); 7.14 (s, 2H); 5.83 (q, 1H); 2.70-2.10 (m, 10H); 2.23 (s, 3H); 1.96 (s, 3H); 1.16 (d, 3H).

Example 32

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-piperidin-4-yl]-N-methyl-acetamide (enantiomer 1)

TFA (2.8 mL) was added to a solution of intermediate 62 (370 mg) in anhydrous DCM (12 mL) previously cooled at 0°C, under a Nitrogen atmosphere. The solution was stirred at 0°C for 2 hours, then it was treated at 0°C with a 10% sodium hydroxide solution until pH=10. The aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were dried, concentrated *in vacuo* to give the title compound as a white foam (370 mg) used as crude in the next step without further purification.

T.l.c.: DCM/MeOH 8:2, containing 1% of conc. NH₄OH, R_f=0.15 (detection with ninhydrine).

MS (ES/+): m/z=513 [M+H]⁺.

Example 33

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide (enantiomer 1)

A solution of formaldehyde in water (37% w/w; 110 μ L) was added to a stirred solution of Example 32 in CH₃CN (8 mL) under a nitrogen atmosphere at 23°C. After 10 min sodium triacetoxyborohydride (230 mg) was added. The mixture was stirred for further 2 hours then it was quenched with a 5% sodium hydrogen carbonate solution (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phases were dried and concentrated *in vacuo*, and the residue was purified by flash chromatography (DCM/MeOH from 9:1 to 8:2, then from 8:2 containing 3% of conc. NH₄OH to 7:3 containing 3% of conc. NH₄OH) to give the title compound (260 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2 containing 1% of conc. NH₄OH, R_f=0.65 (detection with ninhydrine).

MS (ES/+): m/z = 527 [M+H]⁺.

Example 34

(-)-N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide hydrochloride

The compound of Example 33 (246 mg) was dissolved in dry Et₂O (8 mL), cooled to 0°C and treated with hydrochloric acid (1M in Et₂O – 514 μ L). The mixture was stirred at 0°C for 1.5 hours, then it was filtered under a nitrogen atmosphere in a dry box. The solid was washed with Et₂O (2 x 4 mL), and then pentane (3 x 8 mL) to give the title compound (200 mg) as a white solid.

MS (ES/+): m/z=527 [MH-HCl]⁺.

NMR (d₆-DMSO): δ (ppm) 10.02 (bs, 1H); 7.71 (s, 1H); 7.37 (dd, 2H); 7.20 (s, 2H); 7.13 (m, 2H); 5.58 (q, 1H); 3.35 (bm, 2H); 2.96 (d, 1H); 2.9 (d, 1H); 2.82 (dd, 1H); 2.79 (d, 3H); 2.64 (dd, 1H); 2.7-2.5 (m, 2H); 2.25 (s, 3H); 2.07 (dd, 1H); 1.92 (m, 1H); 1.18 (d, 3H).

δ _D: -49.1 (0.5% in MeOH).

HPLC (column: XTerra MSC18 50x4.6mm, 5 μ m; mobile phase: H₂O+0.1% TFA/CH₃CN+0.1 TFA from 90/10 to 10/90 in 12 min.; flow rate=1 mL/min; detection: λ =200-400 nm, ES+: 100-900): retention time = 8.56 minutes; purity (a/a %) >99%.

Example 35

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-piperidin-4-yl]-N-methyl-acetamide (enantiomer 2)

TFA (1.5 mL) was added to a solution of intermediate 63 (310 mg) in anhydrous DCM (6 mL) previously cooled at 0°C, under a Nitrogen atmosphere. The solution was stirred at 0°C

for 2 hours, then it was concentrated *in vacuo* at 0°C. The residue was taken up with a saturated solution of potassium carbonate (10 mL) and diluted with EtOAc (50 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The collected organic phases were dried and concentrated *in vacuo* to give the title compound as a white foam (300 mg) used as crude in the next step without further purification.
T.l.c.: DCM/MeOH 8:2, containing 1% of conc. NH₄OH, R_f=0.15 (detection with ninhydrine).
MS (ES/+): m/z=513 [M+H]⁺.

10 Example 36

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide (enantiomer 2)

A solution of formaldehyde in water (37% w/w; 92 □L) was added to a stirred solution of Example 35 in CH₃CN (6 mL) under a nitrogen atmosphere at 23°C. After 30 min sodium triacetoxyborohydride (181 mg) was added. The mixture was stirred for further 2 hours then it was quenched with a saturated solution of sodium hydrogen carbonate (5 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases were dried and concentrated *in vacuo*, and the residue was purified by flash chromatography (DCM/MeOH from 9:1 to 8:2, then from 8:2 containing 3% of conc. NH₄OH to 7:3 containing 3% of conc. NH₄OH) to give the title compound (225 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2 containing 1% of conc. NH₄OH, R_f=0.65 (detection with ninhydrine).

MS (ES/+): m/z=527 [M+H]⁺.

25 Example 37

(+)-N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide hydrochloride (enantiomer 2)

The compound of Example 36 (220 mg) was dissolved in dry Et₂O (8 mL), cooled to 0°C and treated with hydrochloric acid (1M in Et₂O – 460 □L). The mixture was stirred at 0°C for 30 minutes, then it was filtered under a nitrogen atmosphere in a dry box. The solid was washed with Et₂O (2 x 5 mL), Et₂O/pentane 1:1 (2 x 6 mL) and pentane (2 x 3 mL) to give the title compound (190 mg) as a white solid.

MS (ES/+): m/z=527 [MH-HCl]⁺.

NMR (d₆-DMSO): □ (ppm) 10.02 (bs, 1H); 7.71 (s, 1H); 7.37 (dd, 2H); 7.20 (s, 2H); 7.13 (m, 2H); 5.58 (q, 1H); 3.35 (bm, 2H); 2.96 (d, 1H); 2.9 (d, 1H); 2.82 (dd, 1H); 2.79 (d, 3H); 2.64 (dd, 1H); 2.7-2.5 (m, 2H); 2.25 (s, 3H); 2.07 (dd, 1H); 1.92 (m, 1H); 1.18 (d, 3H).

□□□_D: +50.6 (0.5% in MeOH).

HPLC (column: XTerra MSC18 50x4.6mm, 5 μ m; mobile phase: H₂O+0.1% TFA/CH₃CN+0.1 TFA from 90/10 to 10/90 in 12 min.; flow rate=1 mL/min; detection: λ =200-400 nm, ES+: 100-900): retention time = 8.56 minutes; purity (a/a %) >99%.

5 **Example 38**

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-(4-phenyl-piperidin-4-yl)-N-methyl-acetamide (enantiomer 1)

10 TFA (3 mL) was added to a solution of intermediate 68 (320 mg) in DCM (12 mL) previously cooled to 0°C under a Nitrogen atmosphere. The resulting solution was stirred in these conditions for 1 hour, then a 10% sodium hydroxide solution was added until pH=12. The aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were dried, concentrated *in vacuo* to give the title compound (215 mg) as a white foam.

T.l.c.: DCM/MeOH 8:2 containing 0.5% of conc. NH₄OH, R_f=0.09.

MS (ES/+): m/z=495 [M+H]⁺.

15

Example 39

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-(1-methyl-4-phenyl-piperidin-4-yl)-N-methyl-acetamide (enantiomer 1)

20 Sodium triacethoxyborohydride (276 mg) was added to a solution of Example 38 (215 mg) in anhydrous CH₃CN (10 mL) with a solution of formaldehyde in water (37% w/w, 130 μ L) under a Nitrogen atmosphere. The mixture was stirred at r.t. for one hour, then the solvent was removed *in vacuo* and the residue was dissolved in 5% sodium hydrogen carbonate solution (5 mL) and extracted with DCM (2x10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM, 25 DCM/MeOH from 9:1 to 8:2 containing 0.5% of conc. NH₄OH) to give the title compound (162 mg) as a white solid.

T.l.c.: DCM/MeOH 8:2 containing 0.5% of conc. NH₄OH, R_f=0.43 (detection with ninhydrine).

MS (ES/+): m/z=509 [M+H]⁺.

30

Example 40

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-(1-methyl-4-phenyl-piperidin-4-yl)-N-methyl-acetamide hydrochloride (enantiomer 1)

35 The compound of Example 39 (160 mg) was dissolved in Et₂O (6 mL), cooled to 0°C and treated with hydrochloric acid (1M in Et₂O – 350 μ L). The mixture was stirred at 0°C for 30 minutes, then the solvent was removed *in vacuo* and the residue was triturated with pentane to give the title compound (160 mg) as a white solid.

MS (ES/+): m/z=505 [MH-HCl]⁺.

NMR (d_6 -DMSO): δ (ppm) 9.75 (bs, 1H), 7.69 (s, 1H), 7.45-7.08 (m, 7H), 5.56 (q, 1H), 3.3 (b, 2H), 3.0-1.8 (m, 14), 1.12 (d, 3H).

Example 41

5 N-[1-(3,5-Dichloro-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-piperidin-4-yl]-N-methyl-acetamide (enantiomer 1)

10 TFA (3 mL) was added to a solution of intermediate **64** (270 mg) in anhydrous DCM (12 mL) previously cooled at 0°C, under a Nitrogen atmosphere. The solution was stirred at 0°C for 2 hours, then it was treated at 0°C with a 10% sodium hydroxide solution until pH=10. The aqueous layer was extracted with DCM (2 x 10 mL). The combined organic extracts were dried, concentrated *in vacuo* to give the title compound as a colourless oil (227 mg) used as crude in the next step without further purification.

T.l.c.: DCM/MeOH 8:2, containing 1% of conc. NH_4OH , $R_f=0.07$ (detection with ninhydrine).

15 MS (ES/+): $m/z=423$ $[\text{M}+\text{H}]^+$.

Example 42

20 N-[1-(3,5-Dichloro-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide (enantiomer 1)

A solution of formaldehyde in water (37% w/w; 80 μL) was added to a stirred solution of Example 41 in CH_3CN (8 mL) under a nitrogen atmosphere at 23°C. After 10 min sodium triacetoxyborohydride (170 mg) was added. The mixture was stirred for further 2 hours then it was quenched with a 5% sodium hydrogen carbonate solution (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried and concentrated *in vacuo*, and the residue was purified by flash chromatography (DCM/MeOH from 95:5 to 80:20) to give the title compound (190 mg) as a white solid.

25 T.l.c.: DCM/MeOH 8:2 containing 1% of conc. NH_4OH , $R_f=0.38$ (detection with ninhydrine).

MS (ES/+): $m/z=437$ $[\text{M}+\text{H}]^+$.

Example 43

30 N-[1-(3,5-Dichloro-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide hydrochloride (enantiomer 1)

35 The compound of Example 42 (185 mg) was dissolved in dry Et₂O (6 mL), cooled to 0°C and treated with hydrochloric acid (1M in Et₂O – 465 μL). The mixture was stirred at 0°C for 1.5 hours, then it was filtered under a Nitrogen atmosphere in a dry box. The solid was washed

with Et₂O (2 x 4 mL), and then pentane (3 x 8 ml) to give the title compound (150 mg) as a white solid.

MS (ES/+): m/z=437 [MH-HCl]⁺.

5 NMR (d₆-DMSO): δ (ppm) 10.13 (bs, 1H); 7.43 (s, 1H); 7.36 (dd, 2H); 7.10 (t, 2H); 6.95 (s, 2H); 5.54 (q, 1H); 2.89 (d, 1H); 2.83 (d, 1H); 2.57 (s, 3H); 2.9-2.5 (m, 4H); 2.23 (s, 3H); 2.1-1.8 (m, 4H); 1.14 (d, 3H).

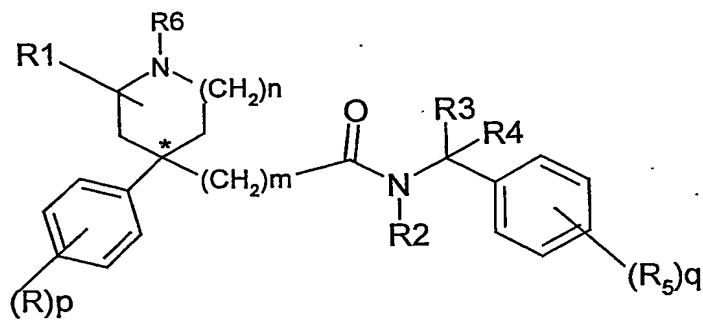
HPLC (column: XTerra MSC18 50x4.6mm, 5 μ m; mobile phase: H₂O+0.1% TFA/CH₃CN+0.1 TFA from 90/10 to 10/90 in 12 min.; flow rate=1 mL/min; detection: λ =200-400 nm, ES+: 100-900): retention time = 8.4 minutes; purity (a/a %) >99%.

10

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example
15 and without limitation, the following claims:

Claims

1. A compound of formula (I)



(I)

wherein

R represents halogen, C₁₋₄ alkyl, cyano, C₁₋₄ alkoxy, trifluoromethyl or trifluoromethoxy;

R₁ represents hydrogen, halogen, cyano, C₁₋₄ alkyl optionally substituted by halogen, or C₁₋₄ alkoxy;

R₂ represents hydrogen, or C₁₋₄ alkyl;

R₃ and R₄ independently represent hydrogen, cyano, C₁₋₄ alkyl or R₃ together with the R₄ represents C₃₋₇ cycloalkyl;

R₅ represents trifluoromethyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, trifluoromethoxy or halogen, cyano;

R₆ represents hydrogen or (CH₂)_rR₇;

R₇ represents hydrogen, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, amine, C₁₋₄ alkylamine, (C₁₋₄ alkyl)₂amine, OC(O)NR₉R₈ or C(O)NR₉R₈;

R₉ and R₈ independently represent hydrogen, C₁₋₄ alkyl or C₃₋₇ cycloalkyl;

m represents zero or an integer from 1 to 4;

n represents 1 or 2;

p is zero or an integer from 1 to 3;

q is zero or an integer from 1 to 3;

r is an integer from 1 to 4;

and pharmaceutically acceptable salts and solvates thereof.

2. A compound selected from:

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide;

N-[1-(3,5-Dichloro-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide;

N-[1-(3,5-Dibromo-phenyl)-ethyl]-2-(1-methyl-4-phenyl-piperidin-4-yl)-N-methyl-acetamide

N-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-2-[4-(4-fluoro-phenyl)-1-methyl-piperidin-4-yl]-N-methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;

5 4-(4-Fluorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide;

4-(4-Chlorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide;

4-(4-Fluorophenyl)-piperidine-4-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;

10 N-(3,5-Bis-trifluoromethyl)-benzyl-2-[(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluorophenyl)-azepin-4-yl]-N-methyl-acetamide;

15 N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

20 N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;

enantiomers thereof and pharmaceutically acceptable salts thereof (e.g. hydrochloride).

25 3. A compound as claimed in claim 1 or 2 for use in therapy.

4. The use of a compound as claimed in claim 1 or 2 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

30

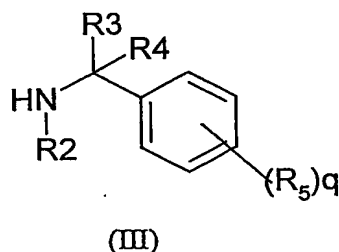
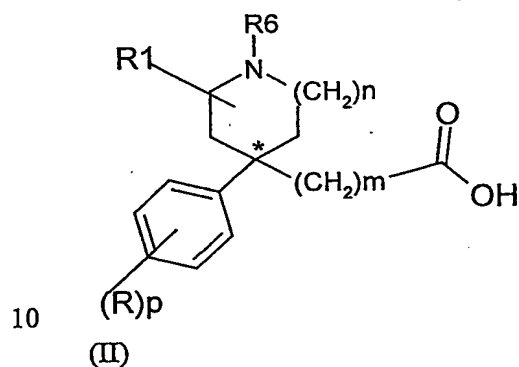
5. The use of a compound as claimed in claim 1 or 2 in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

35 6. A pharmaceutical composition comprising a compound as claimed in claim 1 or 2 in admixture with one or more pharmaceutically acceptable carriers or excipients.

7. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins and/or by selective inhibition of the serotonin reuptake transporter protein comprising administration of an effective amount of a compound of formula (I) as claimed in claim 1 or 2.

5

8. A process for the preparation of a compound as claimed in claim 1 or 2, which comprises reacting an activated derivative of the carboxylic acid of formula (II) wherein R_6 is nitrogen protecting group or $(CH_2)_rR_7$, with amine (III)



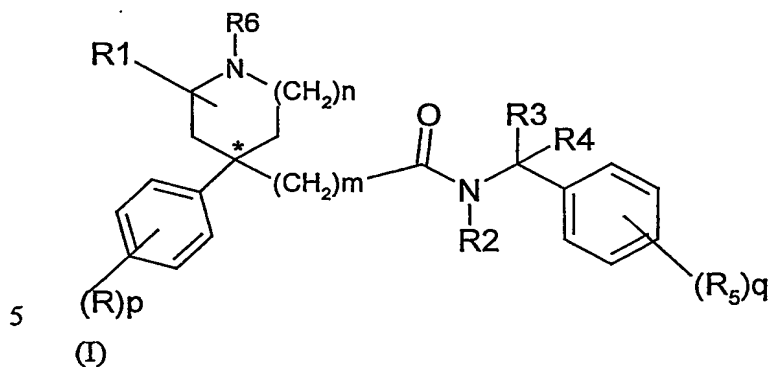
followed where necessary or desired by one or more of the following steps

15

- i) removal of any protecting group;
- ii) isolation of the compound as a salt or a solvate thereof;
- iii) separation of a compound of formula(I) or a derivative thereof into the
- iv) enantiomers thereof.

Abstract

The present invention relates to cyclic amine derivatives of formula (I)



wherein

R represents halogen, C₁₋₄ alkyl, cyano, C₁₋₄ alkoxy, trifluoromethyl or trifluoromethoxy;

10 R₁ represents hydrogen, halogen, cyano, C₁₋₄ alkyl optionally substituted by halogen, or C₁₋₄ alkoxy;

R₂ represents hydrogen, or C₁₋₄ alkyl;

R₃ and R₄ independently represent hydrogen, cyano, C₁₋₄ alkyl or R₃ together with the R₄ represents C₃₋₇ cycloalkyl;

15 R₅ represents trifluoromethyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, trifluoromethoxy or halogen, cyano;

R₆ represents hydrogen or (CH₂)_rR₇;

R₇ represents hydrogen, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, amine, C₁₋₄ alkylamine, (C₁₋₄ alkyl)₂amine, OC(O)NR₉R₈ or C(O)NR₉R₈;

R₉ and R₈ independently represent hydrogen, C₁₋₄ alkyl or C₃₋₇ cycloalkyl;

m represents zero or an integer from 1 to 4;

20 n represents 1 or 2;

p is zero or an integer from 1 to 3;

q is zero or an integer from 1 to 3;

r is an integer from 1 to 4;

and pharmaceutically acceptable salts and solvates thereof and pharmaceutically acceptable
25 salts and solvates thereof, process for their preparation and their use in the treatment of conditions mediated by tachykinins and/or by selective inhibition of serotonin reuptake transporter protein.